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REVIEW

Environmental influences in cancer aetiology

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Abstract
Purpose. The purpose of this review is to inform both scientists and clinicians about the increase in cancer incidence throughout the Western World and to discuss environmental influences in cancer aetiology, in order to stimulate thoughts about plausible aetiological mechanisms and possible preventative measures.
Design. Literature review.
Materials and methods. This review was conducted by searching biomedical databases such as PubMed and Medline. Further research to obtain cancer incidence data involved accessing UK cancer registries, major cancer charities and government statistical records from the Office of National Statistics, the Department of Health, and the Department of Environment, Food and Rural Affairs.
Results. Cancer incidence rates have increased in the Western World and this increased incidence affects the whole age spectrum. Epidemiological studies have provided some evidence of an association between exposure to environmental contaminants such as organochlorines and increased cancer risk. However, many epidemiological studies have been inconclusive. Similar reviews concerning environmental influences in cancer aetiology concluded that exposures to carcinogenic or endocrine-disrupting chemicals exist at concentrations too low or have carcinogenic potential too weak to be considered a major factor in cancer aetiology. However, animal and *in vitro* studies together with epidemiological evidence discussed in this review would dispute that claim; even if healthy adults are not at risk, it would seem that the developing foetus, infant, child and young adults are at risk. In addition, studies discussed in this review show that low oestrogenic potency cannot be used as a marker of the capability of a chemical to cause oestrogenic responses and endocrine disruption. Genetic polymorphisms, which can predispose people to cancer, may interact with environmental contaminants such as organochlorines and endocrine disrupters, thus providing a modifying effect. Prevention measures have hitherto predominately centred on tobacco smoking cessation and diet education. Anecdotal evidence from practising physicians in pre-industrial and traditional living societies, i.e. Canadian Inuits and Brazilian Indians suggests malignant disease was rare. A relatively new theory other than the somatic mutation theory has been proposed, the main premise being that carcinogenesis is a problem of tissue organization, comparable with organogenesis.
Conclusions. It is feasible that chemical environmental contaminants, in particular synthetic pesticides and organochlorines with endocrine-disrupting properties, could be major factors in cancer aetiology, particularly for hormone-dependent malignancies, such as breast, testicular and prostate cancers. Animal and *in vitro* studies provide good evidence of a feasible mechanism whereby environmentally relevant levels of organochlorines and substances of low oestrogenic potency can cause endocrine disruption and consequently malignant disease. In addition, low oestrogenic potency should not be

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used as a marker of the capability of a chemical to cause oestrogenic responses and endocrine disruption. Preventative measures other than education about tobacco, diet and the promotion of physical activity should be considered. Moreover, it seems to be the most vulnerable members of society: the developing foetus, the developing child and adolescent and the genetically predisposed, who are at risk of developing cancer following involuntary exposure to environmental contaminants. This may be an appropriate time for governments to adopt the precautionary principle until substances to which members of society are involuntarily exposed are proved safe from long-term, low-level effects on human health. The World Health Organization estimates that between 1 and 5% of malignant disease in developed countries is attributable to environmental factors: it is possible that this figure may be underestimated. Anecdotal evidence suggests that cancer may be a disease of industrialization. Further research into the tissue organization field theory may be warranted, as some forms of pre-malignant states are attributed to dysorganogenesis, for example an undescended testis.

Keywords: *Cancer incidence, epidemiology, cancer and the environment, organochlorines and cancer, persistent organic pollutants and cancer, cancer aetiology, carcinogenesis*

Introduction

The global burden of cancer is increasing, especially in the developed world. Annually, around 10 million people worldwide will be diagnosed with cancer and a total of 22 million people are current cancer patients. Since 1990, global cancer incidence has risen by 19% [1,2]. According to the World Health Organization (WHO), worldwide cancer rates are set to increase by as much as 50% by the year 2020 unless further preventative measures are put into practice [3].

There is a difference in the distribution of the cancer burden between the developed world (Europe, North America, Australia, New Zealand and Japan) and the developing world (Africa, Latin America, Asia and the Caribbean) (see Figure 1a, b) [1]. The developed world bears the highest cancer burden [1,4]. The incidence of cancer in Europe represents over 25% of the world burden of cancer [5]. The increasing trends for cancer incidence in the developed world can be seen in Figure 2 [6].

The aetiology of malignant disease also differs between the developed and developing world. Twenty-five per cent of cancers in the developing world are a direct result of chronic infection. Infectious agents such as hepatitis B virus, human papillomaviruses and *Helicobacter pylori* are associated with liver cancer, cervical cancer and stomach cancer, respectively. The developed world has a high incidence of tumours that are said to be primarily associated with affluent societies and Western lifestyle, such as lung (tobacco use), breast, prostate and colorectal cancers [1].

In the UK, for the 10 years 1989–1998, some individual tumours such as prostate cancer, breast cancer and non-Hodgkin's lymphoma (NHL) increased in incidence by 38, 18 and 18%, respectively. Tumours such as lung cancer in males, cervical and stomach cancer have decreased in incidence by 24, 36 and 25%, respectively, over the same time period. However, overall cancer incidence has increased by 1.6% in males and 6.3% in females (see Figure 3) [7]. If the age-standardized incidence rate in England and Wales over the past 30 years is considered (1971–1999), the percentage change for some tumour sites is dramatic (see Figure 4a, b) [8]. The risk of developing cancer in the UK is 35% in males, approximately 1 in 3, and 33% in females, again approximately 1 in 3 [7–9]. Cancer Research UK estimates that around 2% of the UK population (1.2 million) are alive with a diagnosis of cancer [10]. In the USA, the lifetime probability of developing cancer is 1 in 2 for males and 1 in 3 for females [11]. The increasing cancer incidence rate is not restricted to any particular age group: cancer incidence is rising across the whole age spectrum. For

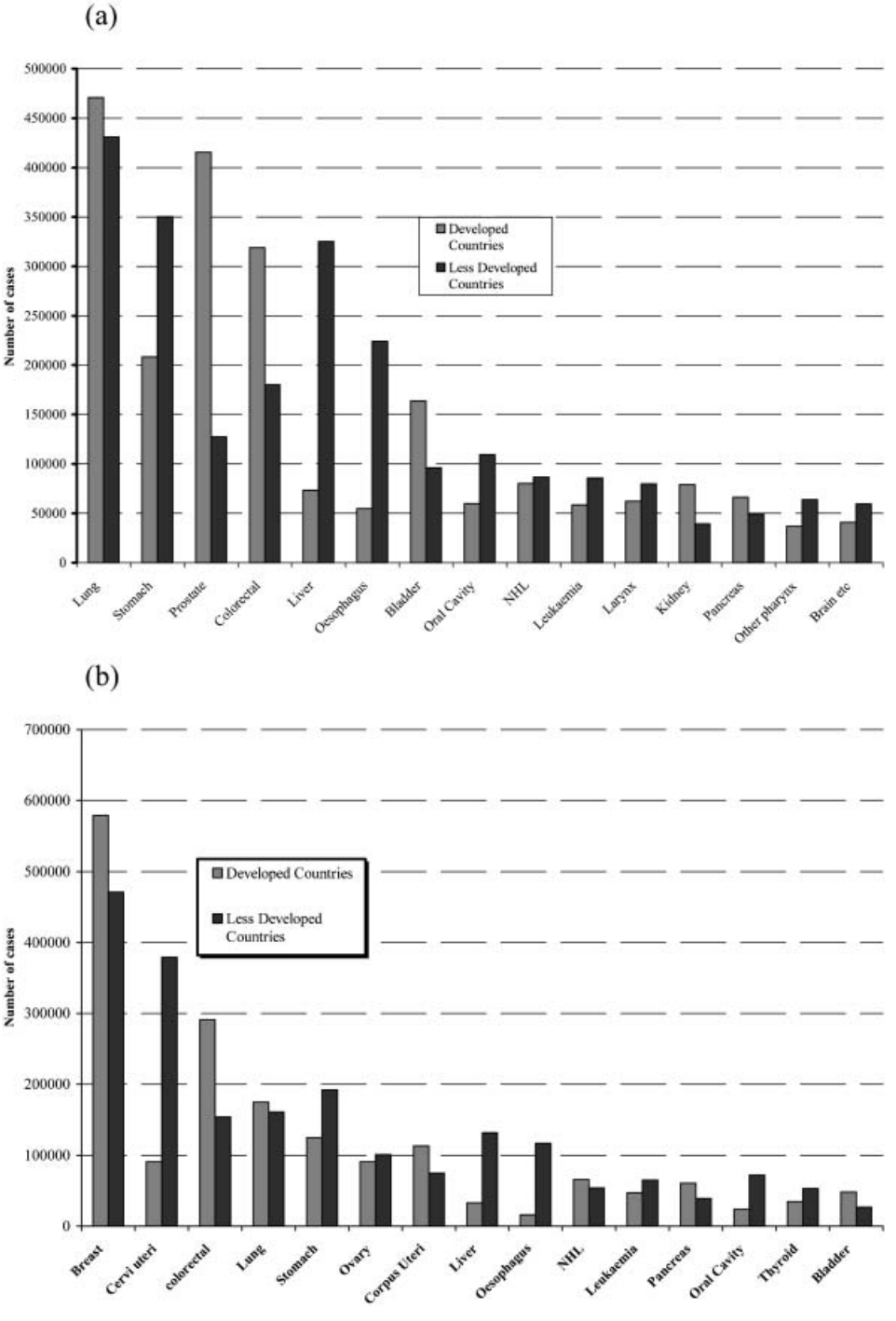

Figure 1. Chart showing a comparison between the number of cancer cases in developed and less developed countries for (a) males and (b) females. Data adapted from [1].

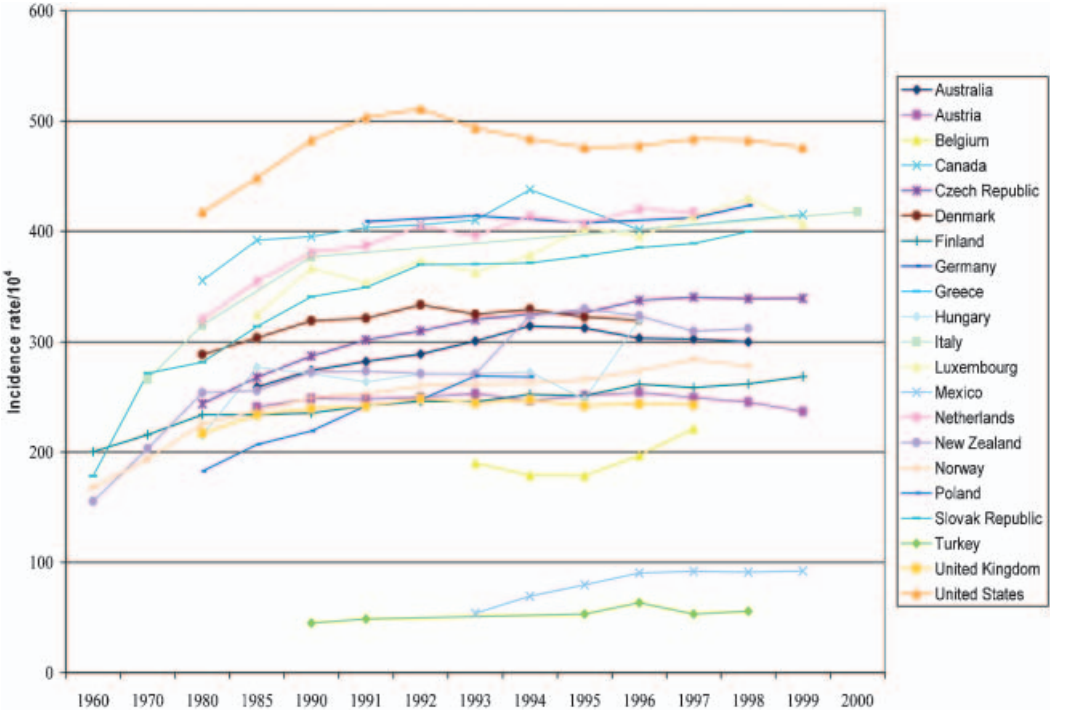

Figure 2. Chart showing an increasing trend over time for cancer incidence rates in developed countries. Data taken from [6].

example, in the UK the overall rate of childhood, adolescent and young adult cancer incidence is increasing by 1.5% per annum [12–14]. Figure 5a, b shows the trend for all malignancies except non-malignant melanoma for England and Wales, 1971–1999, for all ages [15]. In 1971, there were 72,685 and 76,026 cases diagnosed in England and Wales for females and males, respectively. In 1999, there were 119,827 and 116,410 cases of malignant disease diagnosed in England and Wales for females and males, respectively [15]. If age-standardized rates (ASR; refers to the standardized European population) are considered for England and Wales, in 1971 the ASR for females was 243.3 per 10^5 population, and in 1999 the ASR was 343.8 per 10^5 population. The ASR for males was 332.1 per 10^5 population in 1971 and 398.0 per 10^5 population in 1999 (see Figure 5a, b) [15].

There are many factors thought to be involved in cancer aetiology: some are well-established known causes of cancer, others are disputed. For example, the link between tobacco use and lung cancer is well known and undisputed [16–19]. However, any link between environmental pesticide exposure and cancer has conflicting evidence [20–25]. The environment is implicated in the majority of cancers. Two recent studies carried out by Lichtenstein et al. [26] and Czene et al. [27] have demonstrated that environmental influences prevail in cancer aetiology. The results from a study observing concurrent cancer incidence in a cohort of identical twins indicated that the environment rather than genetics predominates in the aetiology of cancer [26]. Czene and colleagues developed a structural equation model to calculate statistically significant estimates of the proportion of genetic

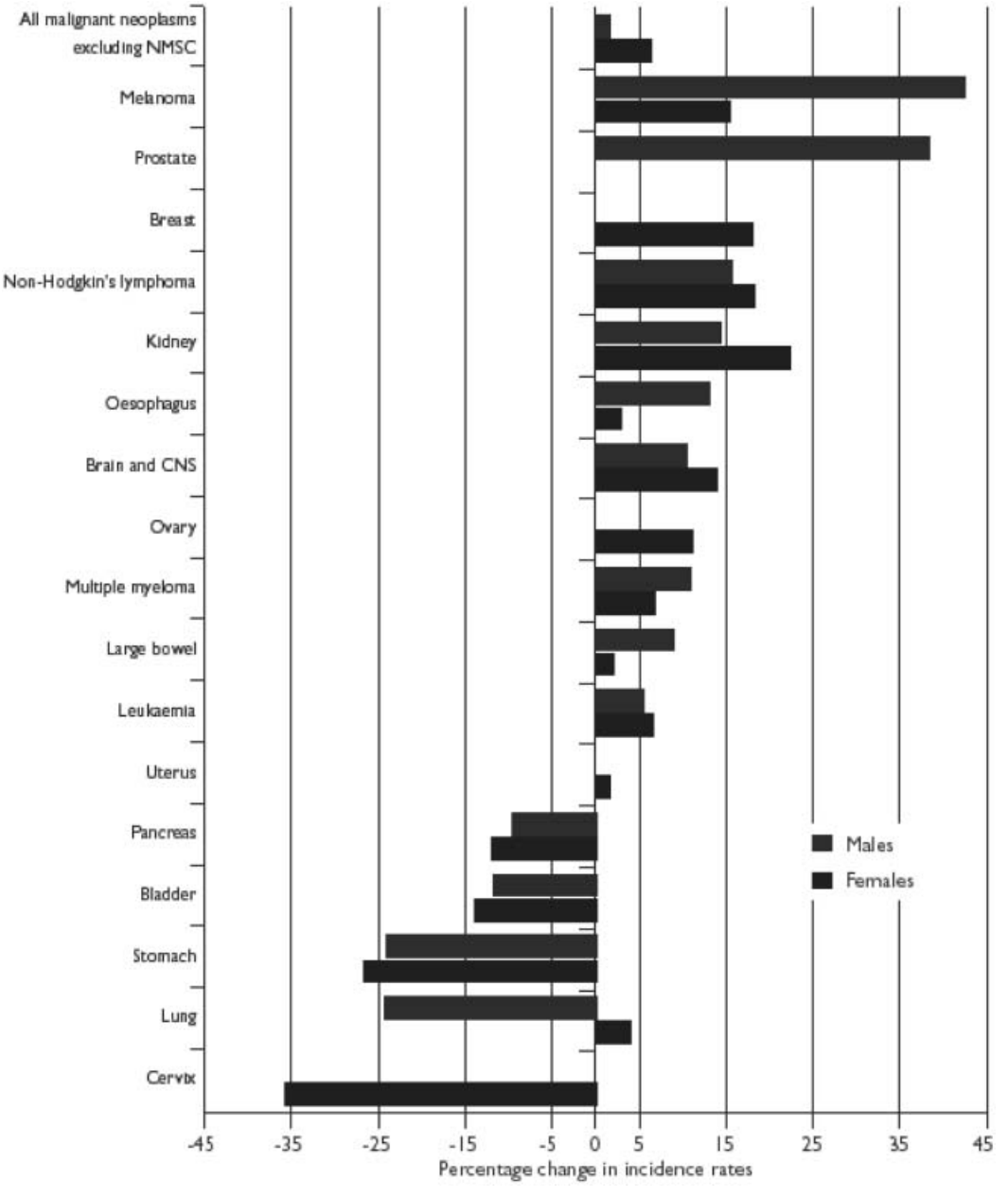

Figure 3. Percentage change in the age-standardized incidence rates of the major cancers by sex, 1989–1998, in the UK. Adapted from [7]. Permission for use granted by Cancer Research UK.

and environmental influences for specific tumour sites. The only tumour site in which genetic influence predominated more than environmental influences was the thyroid [27].

The main factors involved in cancer aetiology are thought to be:

- Tobacco [16–19,28]. Tobacco may be involved in 30% of malignant tumours in the developed world [1].

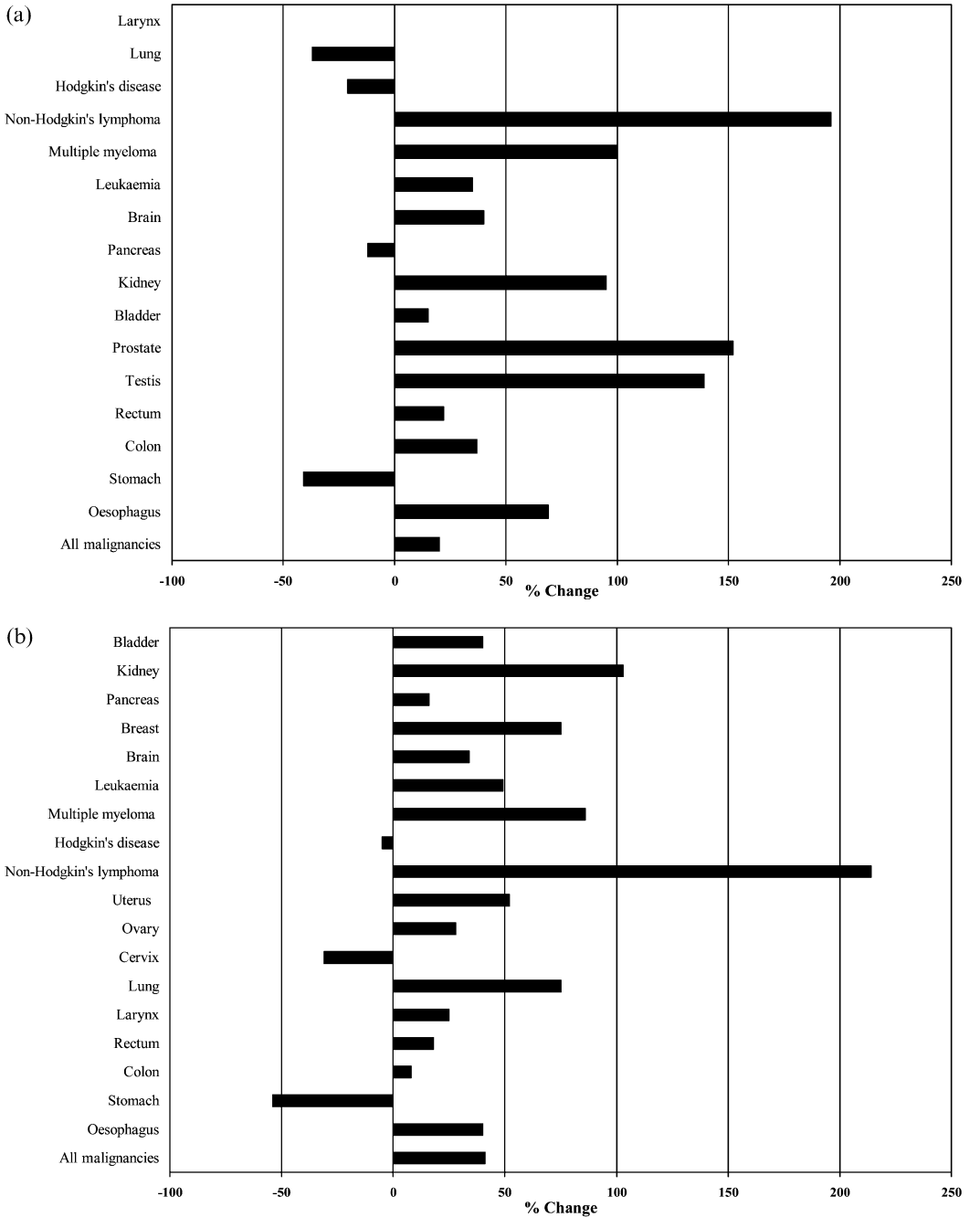

Figure 4. Percentage change in the age-standardized rate in England and Wales, 1971–1999, for (a) males and (b) females for major tumour types. Data adapted from [8].

- Diet [29–36].
- Alcohol [1,37,38].
- Occupation: chemical workers [21], asbestos [39,40], radiation [41–45], benzene [46], dyes [47–50], pesticides [23,51,52], polychlorinated biphenyls (PCBs) [53,54].

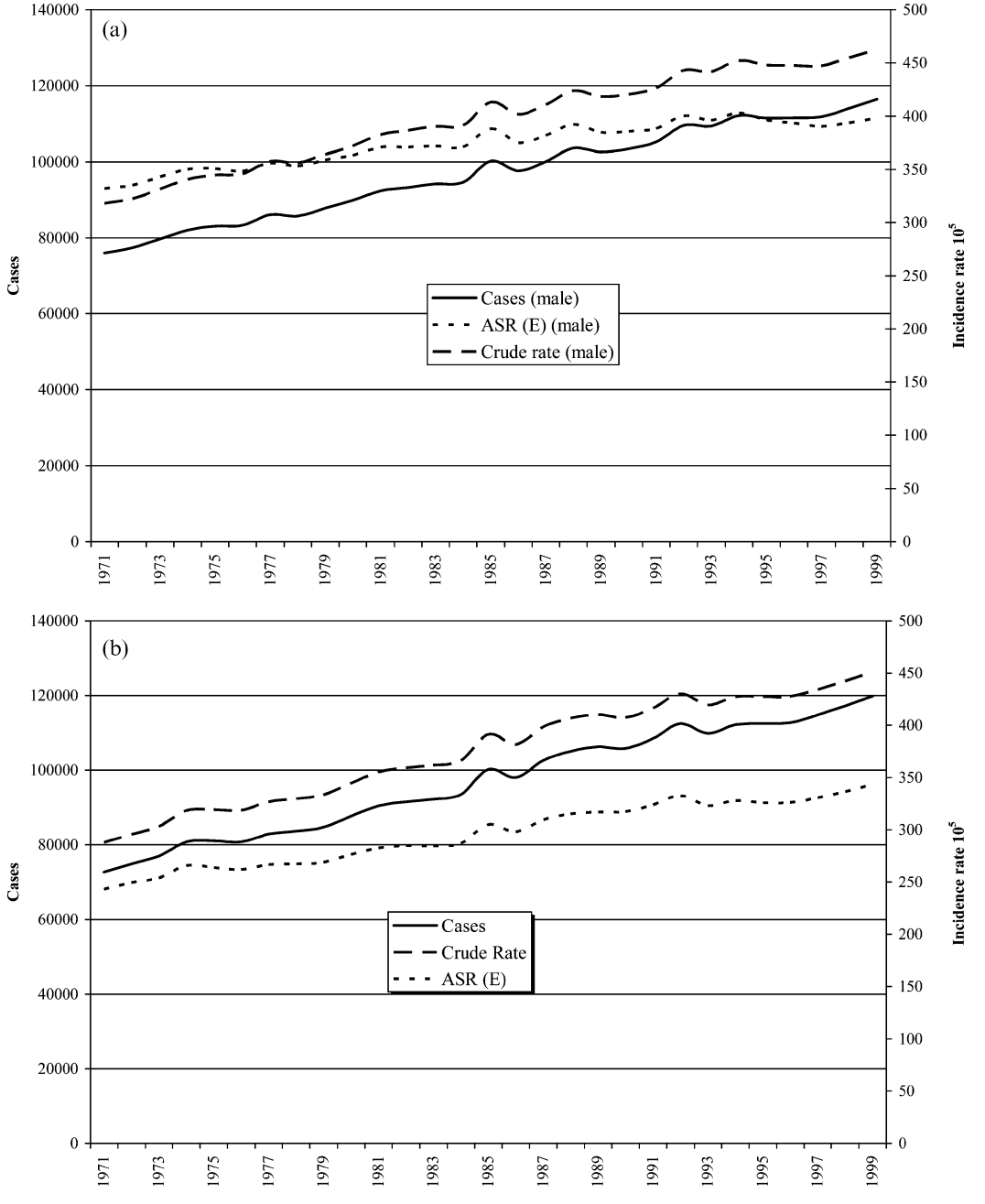

Figure 5. Trend for the incidence rate for all malignancies in England and Wales for (a) males, all ages and (b) females, all ages, 1971–1999 [15].

- Medication: anti-cancer drugs [55], hormone replacement therapy [56].
- Natural sources: radon [57–59], ultraviolet and cosmic rays [1].
- Infectious agents [1,60–63].
- Genetic susceptibility [1].
- Environmental [1,26,64–70].

There is discord between researchers into what has facilitated the rise in cancer incidence worldwide, especially in developed countries. The most widely accepted theory is that the increase in cancer incidence is primarily a consequence of an expanding ageing population [10,11,71–74]. The theory is based on the hypothesis that people are living longer, therefore they have a greater chance of accumulating the necessary mutations needed for malignant transformation of cells, according to the multistage theory of carcinogenesis postulated by Armatage & Doll [75], whereby accumulations of mutations in the order of six or seven are needed for malignant transformation of cells. They argued that cancer increases with old age because of the time it takes to acquire enough mutations to render malignant transformation of a cell. A cytogenetic age-distribution study by Moorman et al. [76] did not fit this model. The age distribution of acute myeloid leukaemia patients who had translocations was constant (see Figure 6) [76]. Ames & Gold stated that increasing cancer incidence trends are a consequence of improved diagnostic techniques and screening [77]. However, delays in reporting cancer incidence and errors in the reporting of the data can lead to unreliable cancer incidence rates. If such data are not adjusted correctly, cancer incidence trends may show bias towards a downward trend [78].

Another theory postulated is that the recent rising trend for cancer incidence may in part be a consequence of involuntary exposure to carcinogens in the environment [65,79–83].

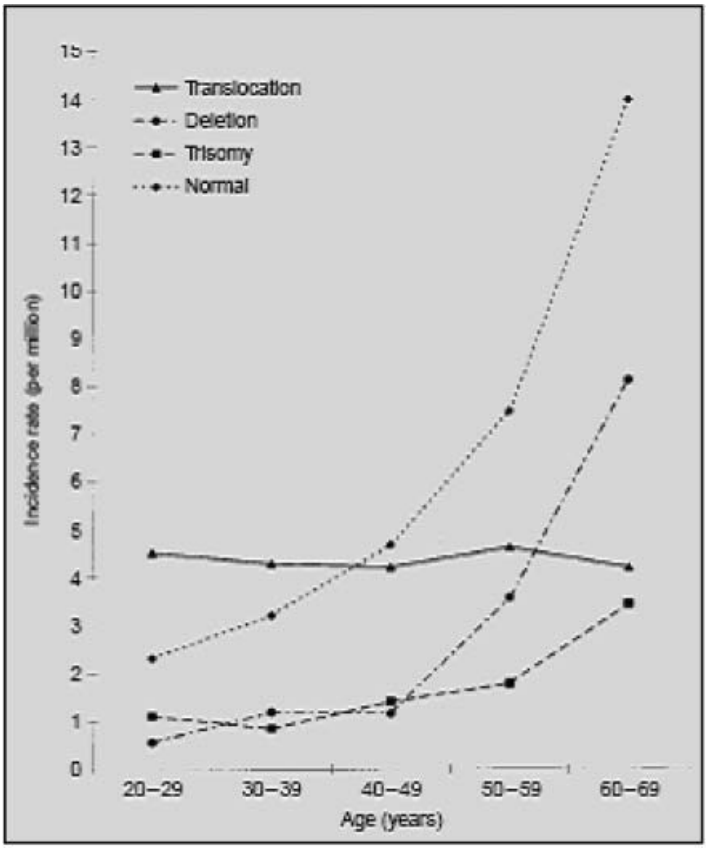

Figure 6. A cytogenetic age-distribution study by Morman et al. [76] showing age-specific incidence rates (per million) for *de novo* acute myeloid leukaemia by karyotype group. Data taken from [76].

This hypothesis is not incompatible with a rising incidence of cancer associated with increasing age. It is widely acknowledged that many environmental pollutants are carcinogens and cancer risk is clearly related to the period of exposure. The International Agency for Research on Cancer (IARC) currently estimates that between 1 and 5 % of malignant disease in the developed world is from environmental pollution [1].

In a broad sense, environmental causes of cancer would include tobacco use, lifestyle, diet and occupation. However, this review will define environmental exposure as involuntary exposure to carcinogens. Involuntary exposure implies that the individual has no control over the level of exposure, for example, exposure by means of the diet or through soil, air and water pollution.

This review will examine the current literature concerning environmental influences in cancer aetiology, with particular emphasis on hormonally mediated cancers such as breast, testicular and prostate cancers. NHL and childhood cancer will also be reviewed. Evidence concerning the historical aspect of cancer will also be addressed.

Methodology

Systematic searches of online biomedical databases such as PubMed, BioMed Central, Science Direct and Medline for current literature concerning environmental factors associated with cancer aetiology were made.

Further research to obtain cancer incidence data involved accessing UK cancer registries, major cancer charities and government statistical records from the Office of National Statistics, the Department of Health, and the Department of Environment, Food and Rural Affairs. Overseas government statistical agencies were also contacted and their data accessed. For example, the Cancer Registry of Norway, Statistics Denmark, WHO, IARC, Environmental Protection Agency and National Cancer Institute (both USA).

Cancer incidence data obtained from these sources have been analysed to facilitate the construction of tables and charts in order to graphically demonstrate cancer incidence rates (crude and age standardized).

Historical aspects of cancer

It is difficult to review the evidence available for the historical aspects of cancer. Has cancer been afflicting humans for millennia or is cancer a modern disease facilitated by anthropological activities? Much of the available evidence is subjective and anecdotal.

The oldest written description of cancer dating back to approximately 1600 BC is recorded on The Edwin Smith Papyrus, which describes eight cases of tumours or ulcers of the breast. The writing goes on to state 'there is no treatment' [84]. However, two other medical papyruses, the Ebers Papyrus and the Kahun Gynaecological Papyrus, do not mention cancer [84,85].

Bone growths found on skeletal remains of mummies, which are indicative of osteosarcoma and skull destruction similar to that found in head and neck cancer, have been discovered. Evidence of malignant melanoma was found on mummified remains of Peruvian Incas, dating back around 2400 years. The oldest specimen of a human cancer was found in a female skull dating from the Bronze Age (1900–1600 BC). However, the oldest evidence of a hominid malignant tumour (Burkitt's lymphoma) was found on the remains of a *Homo erectus* or *Austropithecus* by Louis Leakey in 1932 [84,86–88].

The word cancer was first used to describe malignant disease by Hippocrates. Blood vessels around malignant tumours reminded him of crab claws. The writings of Hippocrates refer to many different cancer sites [84,88].

Through the Middle Ages and up to the eighteenth century there are many references to malignant disease by doctors and pathologists such as Galen, Stahl, Hofman, John Hunter, Johannes Muller, Karl Thiersch and Rudolph Virchow. John Hunter was the first surgeon to suggest that cancer may be cured by surgery [84,85].

In 1761, John Hill documented the danger of tobacco use in a book titled 'Cautions against the immoderate use of snuff'. The first evidence of an occupational cause of cancer came from observations by Percivall Pott in 1775. Pott noticed a high incidence of scrotal cancer among young chimney sweeps, which was caused by soot collecting under their scrotum [84,86–88]. Indisputably, cancer is a disease that has always afflicted humans. However, how prevalent was cancer in ancient times and in the pre-industrial era?

An article by Goldsmith [89] addressed this question. Goldsmith reviewed anecdotal recorded evidence from missionaries and some eminent physicians of the late nineteenth and early twentieth centuries. A major source of evidence concerning the prevalence of malignant disease came from a book by Vilhjamur Stefansson [90]. The book cites evidence obtained from authors who were physicians or missionaries in societies that had not changed their way of life for centuries, i.e. traditionally living people and pre-industrial societies. These authors reported a constant pattern of cancer prevalence: malignant disease was remarkably rare or absent. However, one author, Dr William Seaman Bainbridge, who wrote the paper 'The cancer problem', observed an adverse change in cancer prevalence as the society became more industrialized [91].

Another example cited by Stefansson that is similar to the observations of Bainbridge comes from studies of the Canadian Inuits by Bulkley [92] and Romig [93]. Bulkley claimed that he did not see a single malignancy in 12 years and any increase in prevalence was influenced by civilization. Romig reported that he also did not observe malignant disease among Inuits living a traditional lifestyle. However, cases of malignant disease became common following transition to a 'modern lifestyle'.

Stefansson cites many other reports suggesting that cancer was extremely rare among other traditionally living people. One physician, Dr Eugene Payne, spoke of never encountering one case of cancer in over 60,000 patients in Brazil and Ecuador [94]. A Dr Hoffman reported that cancer of the breast was absent in Bolivian Indian women [95].

These reports suggest that although cancer has always been present, the prevalence of cancer has risen through the industrialization and modernization of society.

Endocrine-responsive tumours

Involuntary exposure to environmental pollutants that may be carcinogenic, with particular emphasis on endocrine-disrupting chemicals

The industrial revolution and the subsequent development of the chemical, nuclear and agricultural industries have produced toxic pollution and novel substances of unknown toxicity. Industry and urbanization resulted in an increase in coal, oil and gas burning, producing toxic smoke and smog. Increasing urban and hospital waste has to be put in landfill sites or incinerated. Chemical production in the last half of the last century produced halogenated molecules such as organochlorines and organofluorines for use in the plastic and pesticide industries as well as others. Evolution has avoided the incorporation of such

molecules in the mainstream of biochemistry and as a consequence they have a general tendency to be toxic to most forms of life: humans were never meant to be challenged by these molecules [68]. The nuclear industry involved in producing nuclear power and the reprocessing of plutonium discharges radioactive waste into the sea and landfill sites. Many of these chemicals and pollutants are carcinogenic and mutagenic to animals and humans.

Organochlorines such as PCBs, dioxins (the most toxic being 2,3,7,8-tetrachlorodibenzo-p-dioxin) and pesticides exhibit endocrine-disrupting properties, as do other chemicals such as phthalates [96–99]. PCBs are no longer produced, but are persistent in the environment and can show oestrogenic activity, possibly indirectly [100,101]. One major source of dioxins is the incineration of halogenated plastics such as polyvinylchloride (PVC). Phthalates are used as plasticizers in PVC products. Organochlorine pesticides are almost wholly banned in most industrialized countries. However, they are persistent in the environment. Dioxins and pesticides such as 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane (DDT) have a molecular structure that shows similarities to oestrogen, and can act at the oestrogen receptor as an agonist or antagonist (see Figure 7a, b) [102,103]. Metabolites of the fungicide Vinclozolin and the DDT metabolite p,p'-dichlorodiphenyl-dichloroethylene (p,p'-DDE) have been found to bind to the androgen receptor and block testosterone-induced cellular responses *in vitro* [104,105]. Dioxins, pesticides, PCBs and phthalates may have the potential to be endocrine disrupting and interfere with developmental processes that are regulated by oestrogenic hormones and their derivatives such as testosterone. Table I shows some endocrine-disrupting chemicals, together with their IARC human carcinogen classification [106].

Organochlorines are ubiquitous in the environment, are lipophilic and bioaccumulate in adipose tissue [54,107–110]. The main source of organochlorine exposure is from the diet: the higher up the food chain, the higher the concentration of organochlorines to body weight [111,112].

There is a myriad of *in vitro* and animal studies on organochlorines that show endocrine disruption and carcinogenicity [96,99,106,113–121]. However, are humans exposed to environmental pollutants in sufficient levels to be a major factor in cancer aetiology? This is a vexed question! Although PCBs, dioxins, pesticides and phthalates have been shown to be carcinogenic in animals, many researchers believe that the background levels of these substances are insufficient to cause adverse effects.

Ames & Gold have written many papers on environmental exposure to chemicals, in which they conclude that synthetic chemicals at background environmental levels do not pose a risk. Testing a chemical to deduce carcinogenicity on animals is carried out at the maximum tolerable dose on adult animals. Ames & Gold suggest that the results of these tests are being misinterpreted to mean that low doses of synthetic chemicals and industrial pollutants are relevant to human cancer. They postulate that high-dose rodent tests result in tissue damage and chronic local cell division, which results in cancer, thus the cancer is due to local tissue damage rather than the chemical. Ignoring this exaggerates risk. At low-dose levels, i.e. levels to which humans are exposed, this chronic cell division does not occur. In a book titled 'Misconceptions about the causes of cancer', Chapter 8 is devoted to misconception nine: Pesticides and other synthetic chemicals are disrupting hormones [77,122,123]. They discuss the findings of Safe, which suggest that human exposure to oestrogenic organochlorine residues is tiny when compared with the dietary intake of naturally occurring endocrine-active chemicals (phytoestrogens) in fruits and vegetables, and therefore any risk to health from synthetic pesticides is minuscule, because far higher levels of natural phytoestrogens are taken in from the diet [124–126]. Despite the reasoning

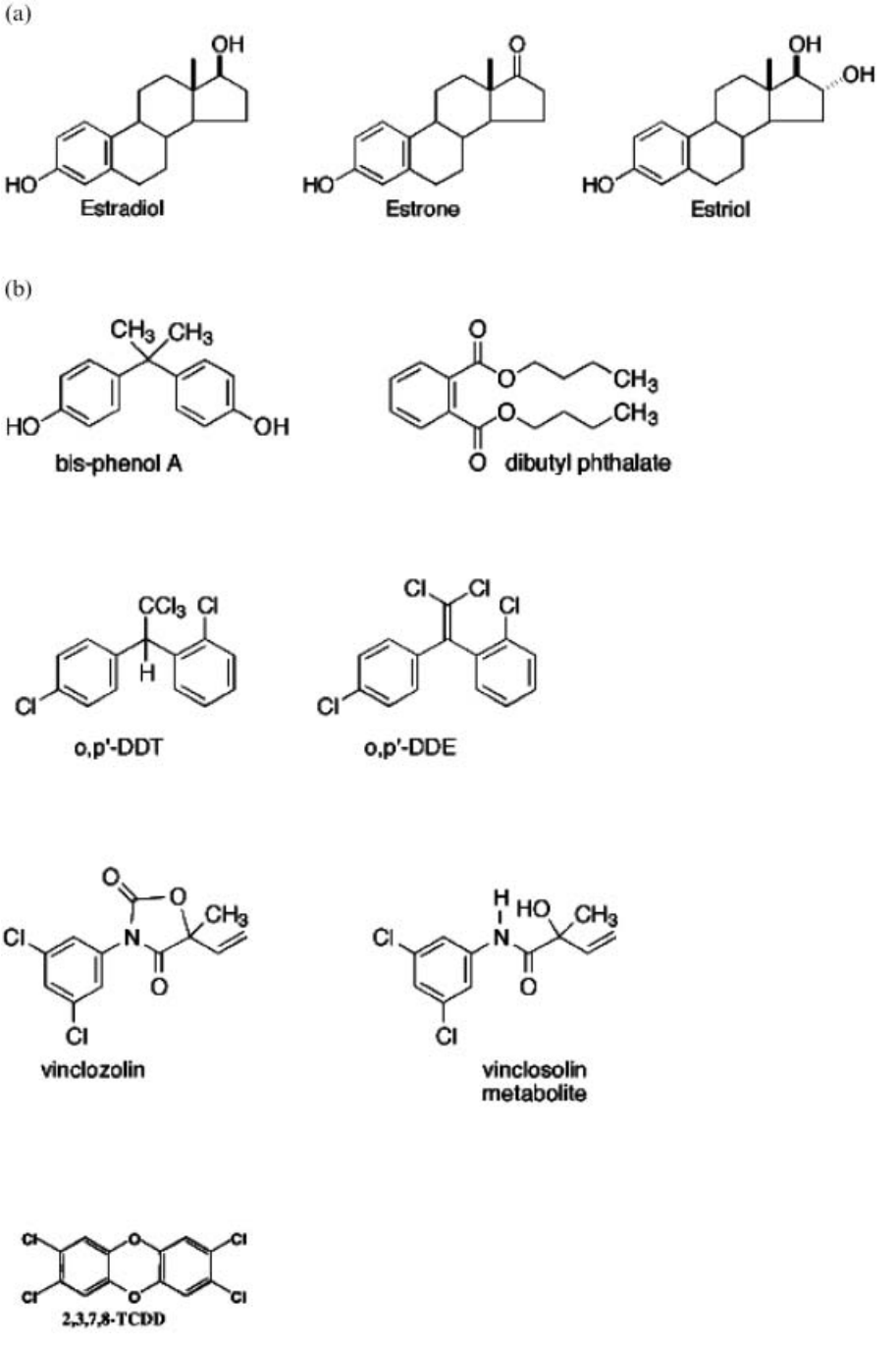

Figure 7. (a) Structure of endogenous oestrogens. Adapted from [102]. (b) Structure of dibutylphthalate, bisphenol A, 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane (DDT), dioxin. The molecular similarity of dibutylphthalate, bisphenol A, DDT, p,p'-dichlorodiphenyl-dichloroethylene (DDE) and dioxin (2,3,7,8-tetrachlorodibenzo-p-dioxin; TCDD) with oestrogen allows the molecules to act at the oestrogen receptor as an agonist or antagonist [102,103]. The DDT metabolite DDE and the vinclozolin metabolite vinclosolin have been shown to bind to androgen receptors [103,104].

Table I. Endocrine disrupters and their carcinogenic classifications. Adapted from [106] (Permission to use table granted by Oxford University Press and the author, Professor Hiroyuki Tsuda, Japanese Journal of Clinical Oncology 33(6)).

	IARC assessment	Humans	Animals
A. Xenobiotics mimicking or antagonizing sex hormones			
1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane (DDT)	2B	I	S
Polychlorinated biphenyls (PCBs)	2B	I	S
Tetrachloro-p-dioxin (TCDD)	1	L	S
Phenols and phthalates			
Butylated hydroxyanisole (BHA)	2B	ND	S
Bisphenol A	3	ND	L
Di(2-ethylhexy) phthalate (DEHP)	3	I	S
1,4-Dioxane	2B	I	S
Tin compounds: tributyl tin (TBT)	ND	ND	ND
Phenylmethyl-substituted siloxanes: cyclotetrasiloxanes	ND	ND	ND
B. Natural compounds mimicking or antagonizing sex hormones			
Isoflavanoids (glucoside conjugates)			
Genistein	ND	ND	ND
Daidzein	ND	ND	ND
Mycoestrogens			
Zearaleone	3	ND	L
Saponin glycosodes	ND	ND	ND
Ligans	ND	ND	ND
C. Substances affecting thyroid function			
Goitrogens			
Aminotriazole	3	I	S
Thiouracil	2B	I	S
D. Modulators causing mineral corticosteroid imbalance			
Glycyrrhizic acid (from liquorice)	ND	ND	ND

IARC, International Agency for Research on Cancer.
IARC assessment (to humans): 1, carcinogenic; 2A, possibly carcinogenic; 3, not classifiable as to its carcinogenicity; I, inadequate evidence; S, sufficient evidence; L, limited evidence; ND, no adequate data.

of Ames & Gold, it is feasible that certain chemicals may well be dangerous at current environmentally relevant levels; this is discussed in a later section.

Xenoestrogens and endocrine disruption

To address the question of whether synthetic xenoestrogens pose a risk to human health, oestrogen metabolism and bioavailability need to be discussed. There are three main endogenous oestrogens produced primarily by the female ovaries: 17β-oestrodiol (E2), oestrone (E1), which is interconvertable with oestradiol, and oestriol (E3), which is synthesized from oestrone, which is thought to be a partial agonist of the oestrogen receptor. 17β-oestrodiol is the most abundant and most potent oestrogen. Following secretion into the blood, the free form of oestrogen is usually only a small fraction of the total oestrogen in plasma: oestrogens are carried bound to various plasma proteins such as albumin and sex hormone binding globulin (SHBG). Bound and free oestrogens in plasma are in dynamic equilibrium [127]. Endogenous oestrogen levels increase during pregnancy.

However, SHBG levels also increase, which means that free oestrogen levels in plasma remain fairly constant. This ensures that maternal oestrogen is not readily bioavailable to the foetus. However, environmental oestrogens do pass freely over the placenta: diethylstilboestrol (DES) crosses the primate placenta in an unconjugated form [128,129]; bisphenol A, PCBs and other organochlorines have been shown to pass directly across the human, primate and F344/DuCrj (Fischer) rat placenta [130–135].

Phytoestrogens are ingested via the diet and there is some evidence that these weakly oestrogenic compounds may confer a protective role against cancer [136–139]. A study by Bradlow and colleagues [140] provides an insight into the possible mechanism by which the relatively tiny amount of synthetic pesticides may be carcinogenic compared with the relatively huge amounts of natural oestrogenic pesticides. They studied the effect of natural and synthetic pesticides on oestrogen metabolism. Oestrogen metabolism proceeds down two mutually exclusive pathways: the catechol pathway, which produces oestrogen-2-hydroxyestrone, and an alternative pathway that yields 16α-hydroxyestrone. The catechol oestrogen-2-hydroxyestrone is weakly anti-oestrogenic and non-genotoxic. However, 16α-hydroxyestrone is a potent oestrogen, tumorigenic, genotoxic and induces cell proliferation. Bradlow et al. studied the ratio of 16α-hydroxyestrone/oestrogen-2-hydroxyestrone in oestrogen receptor-positive MCF-7 human breast cells after treatment with 7, 12-dimethylbenzen[*a*]anthracine (DMBA) and linoleic acid as positive tumorigenic controls; indole-3-carbinol and eicosapentenoic acid as negative controls; and organochlorine pesticides (DDT, Atrazine, γ-benzene hexachloride, Kepone, coplanar PCBs and endosulphans I and II). The results showed that all the organochlorines tested in the study decreased the amount of 2-hydroxyestrone produced and significantly increased the amount of 16α-hydroxyestrone produced by three- to four-fold relative to negative control cells. DDT, Kepone and Atrazine treatment caused a greater conversion to 16α-hydroxyestrone (seven-fold) and lower conversion to 2-hydroxyestrone than the positive controls, which were known carcinogens. Indole-3-carbinol and eicosapentenoic acid treatment resulted in ratios of 1/10 and 1/2 that of DMBA, respectively, indirectly inhibiting 16α-hydroxyestrone production by increasing C-2-hydroxylation [140].

Bradlow et al. pointed out that a previous study had shown that 16α-hydroxyestrone is genotoxic to normal mammary epithelium, and a raised ratio of 16α-hydroxyestrone is associated with breast and other cancers in animals [141]. Conversely, the oestrogen metabolite oestrogen-2-hydroxyestrone has not been found to be carcinogenic and is weakly anti-oestrogenic, and it may even mediate a protective effect [142]. Animal and human *in vivo* studies found that diets rich in compounds that stimulate oestrogen-2-hydroxyestrone, particularly cruciferous vegetables, which are high in indole-3-carbinol, are protective against cancers such as breast and colon cancer [136–138,143,144].

Although the catechol oestrogen-2-hydroxyestrone is not genotoxic, some catechols derived from quinines and semiquinones have been implicated in cancer aetiology. The catechols 4-hydroxyestradiol, 2-hydroxyestradiol and 2-hydroxyestrone are the three most common catechol oestrogens and only 4-hydroxyestradiol has been shown to be carcinogenic in the male Syrian hamster. No evidence has yet been found in humans to suggest that 4-hydroxyestradiol is formed *in vivo* [140].

Ames et al. point out that Americans ingest 5000–10,000 different natural pesticides and their metabolites, many of which have oestrogenic activity, and each day this intake amounts to approximately 1500 mg of natural pesticides; some 10,000 times more than the 0.01 mg of synthetic pesticides ingested per day [124]. However, it may be feasible that the 1500 mg of

natural pesticides (phytoestrogens) may provide a protective effect against cancer and the 0.01 mg of synthetic pesticides may be involved in cancer aetiology, mediated by the mechanism described by Bradlow et al. [140]. In addition, humans co-evolved with plants that produced novel phytoestrogens and were able to adapt to exposure of these compounds by a progressive ability to safely metabolize compounds that may have initially been toxic. Organochlorine pesticides bioaccumulate over time; this infers that the enzymes required for effective metabolism and excretion of such compounds are either inefficient or not present [145]. In addition, it is possible for a single pesticide to have thousands of congeners, making toxicological testing very difficult [146].

The oestrogen receptor binding pocket is relatively open and has therefore been described as promiscuous. Phenolic, planar compounds with two oxygen-containing moieties, which are around 1.1–1.2 nm apart, will fit into the binding pocket. In addition to endogenous oestrogens, non-steroidal compounds, for example, DES and many synthetic environmental oestrogens and plant polyphenols (isoflavones, coumestrol) can act as oestrogen receptor ligands [147]. The oestrogen receptor historically only had to distinguish between natural endogenous hormones and this is the reason for the 'looseness' of the receptor. The looseness of the receptor infers that before anthropogenic activities contaminated the environment, the only compounds that acted as ligands at the oestrogen receptor were natural oestrogens [145].

Changes in the bioavailability of endogenous oestrogens by exogenous oestrogens can also be a factor that modulates oestrogen toxicity. Serum oestrogens are strongly bound to the serum proteins albumin and SHBG, so that around 5% is circulating unbound or free. The bioavailability of oestrogen is determined by the extent of this protein binding. SHBG does not avidly bind to environmental oestrogens and exogenous oestrogenic compounds can affect SHBG binding to endogenous oestrogens, thus providing a mechanism whereby exogenous oestrogen modulates endogenous oestrogen activity [148].

In a review of his 'oestrogen hypothesis', Sharpe examined data relevant to the hypothesis that oestrogenic compounds may perturb male reproductive tract development. Consequently, compounds exhibiting oestrogenic activity may be a factor in testicular dysgenesis syndrome (TDS), a collection of male reproductive tract disorders, such as testicular cancer, cryptorchidism, low sperm count and hypospadias. Compounds that have been identified as environmental oestrogens have weak intrinsic oestrogenic activity. If these are compared with the known oestrogenic transplacental carcinogen DES, Sharpe concluded that it is unlikely that weak environmental oestrogens could induce TDS. His conclusion was based on a study that showed that exposure to DES needs to be at doses in excess of $50\,\mu g\,kg^{-1}\,day^{-1}$ to induce reproductive tract abnormalities [115]. Sharpe stated: 'based on present understanding, it seems unlikely that altered human exposure to weak oestrogenic compounds can account for the possible increasing incidence of male reproductive tract disorders'. However, he added the caveat: 'this must be considered a tentative conclusion; this does not mean that exposure to environmental chemicals can be ruled out as being involved aetiologically in ''testicular dysgenesis syndrome'', as *in utero* exposure of rats to certain phthalates has been shown to induce a remarkably similar constellation of disorders' [149–152].

Sharpe cited recent studies in which the findings suggest that reproductive tract disorders in male rats are a consequence of a perturbed oestrogen/androgen balance and not from absolute levels of androgens and oestrogens. Thus, much lower levels of oestrogens could be capable of inducing adverse effects if concomitantly androgens are suppressed or production is stopped [115,150,153].

A study by vom Saal and colleagues [121] investigated the effects of *in vivo* exposure to high and low (environmentally relevant) doses of oestradiol and DES on the male mouse foetus. They found that low doses of DES (0.02, 0.2 and 2.0 $ng\,g^{-1}\,day^{-1}$) resulted in a significant increase in adult prostate weight and an increase in the number of androgen receptors, when compared with control mice. However, high doses of DES (200 $ng\,g^{-1}\,day^{-1}$) had the opposite effect: prostate weight was significantly lower than control mice and low-dose treated mice. These effects were also observed for oestradiol, resulting in an inverted U-shape dose–response relationship [121].

Most animal testing is carried out on adult animals and with single chemicals. However, humans are simultaneously exposed to many different chemicals in the environment. Mixtures of chemicals could potentially have synergistic or additive effects. Therefore, traditional toxicological testing may not be adequate for assessing the carcinogenic risk of environmental chemicals [68]. Synergistic and antagonistic effects have been shown when 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and PCBs are administered to rats in varying doses [120].

The US Environmental Protection Agency set up a panel to review low-dose environmental chemicals. The doses that the animals received in the tests had to be lower than the usual animal testing doses or dose levels to which humans are exposed. A subpanel reviewing bisphenol A found that several studies gave credible evidence for low-dose effects. The effects included increased prostate weight in 6-month-old mice and advanced onset of puberty in female mice following *in utero* exposure of 2 or 20 $\mu g\,kg^{-1}\,day^{-1}$. In addition, two different strains of rats showed different effects from bisphenol A. F344 rats exhibited low-dose effects on uterine growth and serum prolactin levels. Sprague–Dawley rats exhibited no adverse effects from low-dose bisphenol A [119].

Animals that showed adverse effects to low-dose bisphenol A also showed effects to low-dose DES. Animals that showed no adverse effects to low-dose bisphenol A also had no effects to low-dose DES. However, due to several studies also consistently showing no effects to low-dose bisphenol A, evidence for low-dose bisphenol A is inconclusive. The Environmental Protection Agency has identified areas of research that need to be carried out in order to clarify the situation regarding low-dose bisphenol A [119].

The panel have also reviewed experiments concerning other environmental oestrogens. The definition of a low-dose effect was that a low-dose effect was deemed to have occurred when a non-monotonic dose response (U-shape) resulted in effects that were significant and occurred at a dose lower than the no observed effect level observed by traditional animal testing models. Low-dose effects were observed for oestradiol, DES, merhoxychlor (insecticide), genistein and nonylphenol. For low-dose DES exposure *in utero* at 0.02 $\mu g\,kg^{-1}\,day^{-1}$ there is a clear effect on prostate size in mice. Low-dose genistein exposure *in utero* through to puberty resulted in hypothalamic changes and changes in the mammary tissue of male rats [119].

The review panel concluded that the current testing paradigm needs to be revised. Changes may be needed regarding dose selection, the age when animals are evaluated and the endpoints measured [119].

An example of adverse effects on development following exposure to environmental xenoestrogens is in the form of neurotoxicity. In a recent review, human prenatal exposure to PCBs and their effect on neurodevelopment was studied. The authors found that the neonates had impaired reflexes and at 4 years of age deficits in cognitive skills were observed [154]. Other effects on development by PCBs have been reported over the last 10 or 20 years. Sex ratios in humans and fish are declining [155]; male fish [116] and frogs

[118] are becoming feminized. Some aspects of human development regulated by hormones are showing signs of perturbation. There is increasing incidence of cryptorchidism seen in males [82] and earlier entry into puberty [156].

In human epidemiological studies, many organochlorines, pesticides and other environmental contaminants that show carcinogenic potential following mutagenicity testing have been implicated in cancer aetiology. However, many other studies dispute any link between environmental contaminants such as endocrine-disrupting compounds (except those universally accepted) and cancer aetiology.

Endocrine disruption is just one example of a possible environmental factor that may or may not be involved in cancer aetiology. Other examples include low-level radiation around nuclear installations and coastlines, electromagnetic forces and radon exposure from anthropological activity. In addition, there may be many possible carcinogenic compounds to which people are exposed in household products. This could be construed as voluntary exposure. However, this may be due to a lack of education about specific products or people may have no alternative but to use a product that may contain even a small carcinogenic risk. For example, aromatic amines in permanent hair dyes were shown to increase the risk of bladder cancer by 3.3-fold among regular users relative to non-users in a study by Gago-Dominguez et al. [49]. Occupational exposure to hair dyes was shown to increase bladder cancer risk by five-fold in people who had worked 10 or more years as hairdressers or barbers. A follow-up study showed that the increased risk was confined to people showing the N-acetyltransferase-2 (NAT2) slow acetylator phenotype [48]. However, Nohynek et al. [157] concluded that 'the weight of evidence suggests that consumer or professional exposure to hair dyes poses no carcinogenic or other human health risks'.

Underarm cosmetics have recently been implicated in the aetiology of breast cancer. Darbre [158] proposed the hypothesis that the chemical constituents of deodorant cosmetics applied to the underarm area can cause breast cancer. Darbre based this hypothesis on observations showing a disproportionately high incidence of breast cancer in the upper outer quadrant of the breast and that the left breast is more prone to the development of cancer than the right breast in both females and males. Darbre implicated parabens as the possible carcinogenic agent in underarm cosmetics. An editorial by Harvey [159] reviewed Darbre's hypothesis and concluded that: 'without clear evidence that using weakly oestrogenic compounds in underarm cosmetics is safe; it may be prudent to apply a precautionary principle and replace known oestrogenic formulation excipients and also, in the case of preservative removal, accept shorter shelf lives'.

Breast cancer

Breast cancer incidence

Worldwide, breast cancer accounts for 10% of the total cancer burden, with an incidence rate of 1,050,000 cases year^{-1} [1]. Almost all cases are found in women; men are 100 times less likely to develop breast cancer [160]. Breast cancer is now the most common cancer among women in developed and developing countries and is described as an epidemic in the world cancer report 2003 [1,161,162]. Worldwide, over a 20-year period, the estimated number of breast cancer cases has doubled [160]. In 1998, the UK breast cancer incidence rate replaced lung cancer as the most common cancer in women and became the most common cancer overall; 15% of the total. In the UK, in 2000 the ASR for breast cancer was 113.9 per 10^5; in terms of cases, there were 40,470 breast cancers diagnosed (30% of all

cancers in women). The total number of breast cancer cases diagnosed was 40,707; males accounted for 240 of these cases [10].

In England and Wales in 1999, the ASR was 116.9 per 10^5; there were 36,438 cases of breast cancer diagnosed. In 2000, the ASR was 114.0 per 10^5 and there were 33,829 cases diagnosed [15]. However, this fall in incidence rate must be treated with caution because not all the breast cancer cases may have been registered. There is evidence that cancer registries can take many years to fully collate cancer incidence data. Swerdlow [163] found that late registrations can affect published incidence data. Incidence data have been added to publications up to 7 years after data have first been extracted for publication. In the 10 years 1989–1998, breast cancer incidence rose by 18% in the UK. In England and Wales in the period 1971–1999, the percentage change in the ASR of breast cancer was 75% [7,8]. Figure 8 shows the trend for cases, and rates of breast cancer in England and Wales, 1971–1999 [15]. In 1950, the chance of a diagnosis of breast cancer was 1 in 20. In 2000, the risk was 1 in 8 [164]. Breast cancer incidence has been shown to be rising in all of 16 European countries in a study by Botha et al. [165].

Geographical variations and socio-economics are important in breast cancer aetiology [166]. Breast cancer risk is highest in affluent societies: the highest rates are found in North America, Europe and Australasia; the lowest rates are found in Africa and Asia [1,161,162].

Factors involved in breast cancer aetiology

The risk factors involved in breast cancer aetiology include: null parity, late first birth, lack of breast-feeding, early menarche, late menopause, long-term oral contraceptive use, hormone replacement therapy, high calorific diet with reduced physical activity (obesity), alcohol, familial history (BRCA1, BRCA2 and p53 germline mutations), radiation

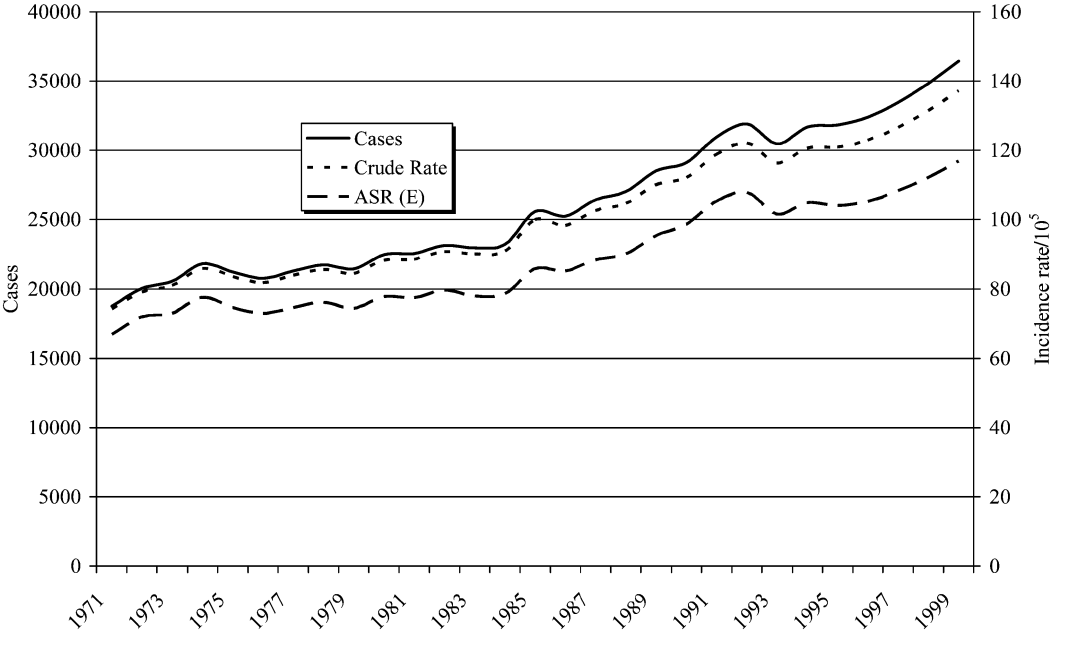

Figure 8. Trend for cases, crude rate and age-standardized rate (ASR) for breast cancer in England and Wales, 1971–1999. Data taken from [15].

[1,161,167–169]. Epidemiological studies on migrants from countries with a low incidence to countries with a high incidence who subsequently developed breast cancer suggest that environmental factors play a role [1,162,170]. The Westernization of areas within Asia has also been suggested to be involved in the aetiology of breast cancer [171]. High levels of endogenous oestrogen have been implicated in an increased risk of breast cancer [172,173]. In one study in the USA, the well-established risk factors for breast cancer accounted for 47% of cases in the study and 41% of cases in the USA [174]. This suggests that in over half of breast cancer cases, the aetiology is unexplained. Other putative factors are exposure during breast tissue development to environmental contaminants of air, soil and water, such as pesticides, organochlorines, dioxins, PCBs and hexachlorobenzene (HCB). All of these have shown evidence of endocrine-disrupting properties that may directly or indirectly interfere with hormone pathways. Extensive research has taken place into such environmental contaminants to elucidate their possible link with the aetiology of breast cancer. Animal evidence has shown an association between environmental contaminants such as organochlorines and the risk of breast cancer. In addition, endocrine-disrupting substances have been shown to disrupt mammary gland differentiation and development following pre-, peri- and postnatal exposure. This evidence is discussed in a later section (Prenatal Exposure).

Environmental factors and breast cancer aetiology

In 1976, in Seveso, Italy, an industrial explosion resulted in environmental contamination of dioxins: up to 30 kg of the chlorinated dioxin TCDD was deposited in the local environment. Studies examining possible links to the risk of breast cancer in Seveso (10- and 15-year follow-up studies) found no increased risk for breast cancer incidence. However, a 20-year follow-up found a statistically non-significant increased risk for breast cancer mortality among women who lived in the most heavily contaminated areas, which suggested a wide range of individual TCDD exposure within zones. A study examining individual TCDD exposure using data from the Seveso Women's Health Study found serum TCDD levels for cases who lived in the most contaminated areas ranged from 13 to 1960 ppt. Statistical analysis showed a dose-dependent risk for breast cancer: the hazard ratio for breast cancer associated with a 10-fold increase in serum TCDD levels was significantly increased to 2.1. The authors stated that these results should be considered an early finding because the cohort study was relatively young; the average interview age was 40.8 years [175]. Further epidemiological studies on populations exposed to background levels of environmental contaminants have shown inconsistent and conflicting results.

Epidemiological studies

Epidemiological studies conducted in Long Island, New York, provide an example of these conflicting studies. Long Island has the highest rate of breast cancer in New York State, which causes public concern. Stellman and colleagues [176] conducted a study to determine whether there was an elevated risk for breast cancer associated with organochlorine adipose tissue concentration. They found that adipose tissue concentrations of the organochlorine compounds DDE, PCBs and total pesticides, which included seven species, were not elevated among controls or cases. In addition, no evidence of a dose–response relationship for the organochlorine compounds analysed was found (a significant dose-related increase in risk was observed for the PCB congener 183, which is heptachlorinated). The results conflicted with a previous study, which found an association

between breast cancer risk and levels of PCB congener 118; Stellman and colleagues did not reproduce this result. The mean adipose levels of DDE, total pesticides and PCBs did not differ between control residents from Queens and Long Island. However, interestingly in an individual analysis of β-hexachlorocyclohexane (β-HCH) and PCB congener 167, there were significant differences in the mean levels between controls from Queens and Long Island (250 of the control women had benign breast disease) [176]. Although the authors found no association between serum organochlorine levels and an elevated risk for breast cancer, they were concerned that all of the samples showed detectable levels of pesticides and PCBs. This gives cause for concern because pesticides and PCBs have been implicated in the aetiology of a number of other cancer types.

A second study, which made use of blood taken from women from a population-based case–control study conducted on Long Island in order to analyse serum organochlorines, found no association between organochlorine exposure and elevated breast cancer risk. The organochlorines analysed included the pesticides DDE, chlordane and dieldrin. The sum of the four most frequently occurring PCB congeners 118, 153, 138, and 180 was also analysed. In addition, no elevated risk was found for organochlorine exposure among women who were overweight, postmenopausal or long-term residents of Long Island [177]. However, a recent study by Muscat and colleagues [178] in Long Island, which examined adipose concentrations of organochlorine compounds instead of serum organochlorine compounds, found an increased risk of breast cancer recurrence.

As outlined earlier in this section, epidemiological studies investigating associations between exposure to environmental contaminants and an elevated breast cancer risk have produced conflicting results, but have provided valuable data and information for further studies. Breast cancer has probably been the most widely investigated tumour and a link between environmental factors and elevated breast cancer risk has been suggested.

Helzlsouer et al. [179] conducted a nested case–control study in 1999 utilizing women who had donated blood in the 1970s. The study found no association between serum concentrations of DDE, the primary metabolite of DDT, and PCBs and the development of breast cancer up to 20 years later.

Zheng and colleagues [180] carried out a study examining breast adipose tissue HCB levels and breast cancer risk. There was no significant difference in adipose tissue levels of HCB between breast cancer patients and controls with benign breast disease. However, these results could be flawed because the controls were not randomly picked non-breast cancer patients: they were patients with benign breast disease. In addition, the authors reported difficulty in obtaining equal sample sizes from benign breast disease patients and breast cancer patients. In this study, HCB levels were higher in postmenopausal women than in premenopausal women.

A prospective study by Dorgon et al. [181] using the Columbia, Missouri Breast Cancer Serum Bank found no overall association between serum organochlorines (PCBs and pesticides) and elevated breast cancer risk. The results suggested that increased serum levels of organochlorine pesticides (DDT) and PCBs (total) did not increase the risk of breast cancer. However, a positive association was suggested for PCB congeners 118 and 138 when blood was collected close to the time of diagnosis. There was also a significant positive association for HCB, although no dose–response relationship was found. They found no association between DDT and total PCB. The overall conclusion was that the organochlorine compounds analysed were not associated with an increased risk of breast cancer [181]. However, congener-specific studies do show an association: exposure to dioxin-like PCBs increases breast cancer risk.

In a study by Demers et al. [182], the most abundant and persistent PCB congeners (PCB 138, PCB 153, PCB 180) were not linked to breast cancer risk. However, PCB 118 and PCB 156 were individually related to risk. Breast cancer risk was also associated with a total concentration of the three mono-ortho-substituted congeners 105, 118, and 156. An earlier study by Demers et al. [183] suggested that organochlorine exposure may affect the aggressiveness of breast tumours, for example, the risk of lymph node involvement may be increased.

A Norwegian study found no association between organochlorines and increased breast cancer risk [184]. However, the body mass index (BMI) data for the participants were not available to the authors; BMI has an inverse relationship with PCB concentration in serum. Nor did the authors have data on menopausal status. However, they did find an interesting result. Some organochlorines were at lower levels in cases than in controls. Could changes in metabolism in cancer patients be responsible for the difference in organochlorine serum levels compared with controls? Also, the PCB congeners with the most oestrogenic potential are the ones most quickly metabolized. This therefore poses a problem for human studies.

Serum samples taken from women diagnosed with breast cancer and healthy control women in a study by Charlier et al. [185] suggested that certain persistent pollutants may occur in higher concentrations in breast cancer patients than in controls. Charlier et al. found that mean serum levels of total DDT (all DDE and DDT isomers) and HCB were significantly higher for women with breast cancer when compared with control women. In addition, no differences in serum levels of DDT or HCB were found between oestrogen receptor-positive and oestrogen receptor-negative breast cancer patients. Conversely, a study by Hunter et al. [186] found that exposure to high levels of DDE and PCBs was associated with a non-significant lower risk of breast cancer. The median level of DDE was lower among case patients than controls (4.71 vs. 5.35 ppb). Similarly, the median level of PCBs was 4.49 vs. 4.68 ppb for patients and controls, respectively [186].

Many of the epidemiological studies discussed above concerning environmental exposure to organochlorines and the risk of breast cancer are inconclusive. However, improved standardization of studies may help to lead to results that are more conclusive. Studies on human cell lines provide evidence that suggests an association between environmental contaminants and increased breast cancer risk. This is discussed below.

In vitro *studies on human breast cancer cell lines have shown associations between environmental contaminants and breast cancer*

The tumour suppressor gene BRCA1, which has a role in cell-cycle control and genetic stability in DNA repair, is often down-regulated in sporadic breast cancers. The down-regulation is not thought to be a consequence of a mutation in BRCA1. Expression of BRCA1 is induced by 17β-oestradiol [187,188]. A study by Rattenborg and colleagues [187] examined the effect on BRCA1 expression of TCDD and the PCBs 158, 180. A reporter gene construct carrying the BRCA1 promoter in human breast cancer cell lines MCF-7 (oestrogen receptor positive) and MDA-MB-231 (oestrogen receptor negative) was used to measure the expression of basal BRCA1 and 17β-oestradiol-induced expression. The results from the reporter gene showed that TCDD and the three PCB congeners reduced both basal and 17β-oestradiol expression in both cell lines. These results were confirmed by Northern blot analysis of BRCA1 mRNA in MCF-7 cells. However, the Northern blot analysis of BRCA1 mRNA in MDA-MB-231 cells showed no effect from the TCDD and the three PCB congeners, which suggested the primary

mechanism of action was via the oestrogen receptor. Because the organochlorines tested increased BRCA1 promoter activity, other mechanisms of action must also be considered. The authors concluded that the anti-oestrogenic effect and subsequent down-regulation of BRCA1 could impair DNA repair, cell-cycle control and stress-induced apoptosis and may therefore affect the risk of breast cancer [187]. Another study using the human cell line MCF-7 showed that exposure to β-HCH promotes epigenetic transformation and invasiveness of these cells. β-HCH is a contaminant of the pesticide lindane, which is still in use in the USA. The cells were exposed to β-HCH for 13 months, which resulted in cells with transformation tendencies and transformation-related biochemical changes. The levels of β-HCH used in the study were comparable with levels found in breast adipose tissue [189].

Bradlow and colleagues [140] studied the effect of natural and synthetic pesticides on oestrogen metabolism in MCF-7 human breast cells. This study is discussed in the Xenoestrogens and Endocrine Disruption section of the review. The results suggested a plausible mechanism by which relatively minute amounts of synthetic pesticides compared with natural pesticides could cause cancer [140]. The authors point out that a previous study had shown that 16α-hydroxyestrone is genotoxic to normal mammary epithelium, and a raised ratio of 16α-hydroxyestrone is associated with breast and other cancers in animals [141].

A recent review by Coyle [190] describes a study by Martin and colleagues [191] using MCF-7 breast cancer cells, in which the divalent ions cadmium, copper, cobalt, nickel, lead, mercury, tin and chromium, together with arsenic, selenite and vanadate were shown to have oestrogenic activity. The metals activated responses that were mediated by oestrogen receptor α and the metallo-oestrogens were found to have a greater potency than phytoestrogens [191]. A further experiment by Johnson and colleagues [192] investigated the effect of environmentally relevant levels of cadmium on the whole animal. They found that low-dose cadmium induced oestrogen responses in female rats such as increased uterine weights, hyperplasia and hypertrophy of the endometrial lining, and increased mammary epithelial density.

Could genetic polymorphisms make people more susceptible to cancer following exposure to environmental contaminants such as xenoestrogens?

A study carried out to examine the interaction of PCBs with the CYP1A1-MspI and exon 7 polymorphisms among 367 breast cancer case–control pairs, of which 293 were postmenopausal pairs, in the Nurses' Health Study, concluded that more studies are required on people who may be genetically susceptible to xenoestrogen exposure [193]. The enzyme CYP1A1 has been shown to be induced by PCBs and DNA adducts may form following exposure to PCBs via a pathway involving CYP1A1 [194]. The results of the study showed no evidence of an association of either the variant CYP1A1 genotype or exposure to PCBs with breast cancer risk. In addition, there was no evidence of an association between PCBs and the risk of breast cancer for women with CYP1A1 homozygous wild-type. However, the results did show a borderline statistically significant increased risk of postmenopausal breast cancer among women with high serum PCB levels and at least one variant allele of the CYP1A1-exon 7 genotype when compared with women homozygous for the wild-type allele and with the lowest levels of PCBs [193].

A study by Hoyer et al. [195] was the first to examine whether mutations in the tumour suppressor gene *p53* affected organochlorine exposure-related breast cancer risk and survival. The study involved analysing for serum concentrations of organochlorines, which

included DDE, DDT, dieldrin and total PCBs, which were compared between cases and controls while stratifying by *p53* mutation status. The results showed a non-significant three-fold increase in the risk of breast cancer associated with the highest exposure level of dieldrin and PCBs among cases with *p53* mutations. However, for DDT and DDE exposure, no difference was found for breast cancer risk between cases with or without mutant *p53*. When the prognostic value of *p53* mutation status and organochlorine exposure was considered, for example relative risk of dying, the only significant result appeared for dieldrin exposure among cases with 'wild-type' *p53*. The results showed a lack of prognostic value according to *p53* status following organochlorine exposure. However, the results suggested that there is an increased risk of breast cancer in women exposed to dieldrin and total PCBs with mutated *p53* status. The authors concluded that the study suggested that *p53* may have a modifying effect on organochlorine influence on breast cancer risk [195].

In vivo *and* in vitro *studies examining organochlorine exposure and breast cancer risk*

The evidence discussed above was largely based on adult exposure to organochlorines. However, as discussed in detail in a later section, *in utero* exposure to organochlorines or exposure at a time when female secondary sexual development is occurring, may be involved in breast cancer aetiology. During development, high rates of cell proliferation and differentiation leave the child's cells prone to mutagenic and epigenetic alteration.

Preliminary findings from a study by Palmer and colleagues [196] suggest that women exposed to DES *in utero* may have an increased risk of developing breast cancer later in life. However, the results were not statistically significant. The cohort was of mean age 43 years, so the authors will be conducting a further follow-up.

In vivo studies using rodents have indicated that exposure to dioxin and other organochlorines *in utero* may predispose female offspring to breast cancer. Dioxins can disrupt endocrine systems and interfere with the proliferation and differentiation of mouse and rat mammary glands. In addition, dioxin can expand the time that a foetus is most sensitive to prospective carcinogens. Dioxin exposure *in utero* may predispose female rodent offspring to mammary gland cancers. A study by Brown et al. [197] examined the effect of *in utero* TCDD exposure and the subsequent effect on rat mammary glands. The results showed TCDD-exposed offspring had increased terminal end buds at sexual maturity when compared with controls (terminal end buds differentiate to form lobules; lobules form the structures required for lactation). Terminal end buds are susceptible to carcinogens because of increased proliferation, as discussed above [197]. A study by Fenton et al. [198] was able to define the developmental window when dioxin exhibited these effects. TCDD exposure at gestation day 15, just after organogenesis, resulted in perturbment of mammary tissue development. However, TCDD exposure at gestation day 20 and postnatal day 5 did not result in any alteration of mammary tissue development. However, are these effects observed in rodents pertinent to environmentally relevant exposure levels of xenoestrogens?

Markey et al. [199] demonstrated that *in utero* exposure to environmentally relevant levels of bisphenol A resulted in perturbed mammary tissue development similar to that found following *in utero* TCDD exposure. The exposed mice had increased terminal ducts and terminal end buds when compared with controls, which predispose the mice to mammary gland cancers later in their adult life. The mice used were CD-1 mice, which are a strain that demonstrates particular resistance to the effects of oestradiol [199].

An alternative theory to the somatic mutation theory (SMT) is the tissue organization field theory (TOFT). In its earliest form, the TOFT was originally known as the morphogenetic field concept, which became the basic model of embryology. Soto & Sonnenschein [200,201] reinterpreted the theory, which is now known as TOFT.

The SMT, proposed by Boveri in 1914 [202], assumes that the default state of cells is quiescence and carcinogenesis occurs at the cellular level. The assumption that the default state of cells is quiescence probably arose from the fact that historically it was difficult to propagate metazoan cells *in vitro* in defined media; this may have led researchers to look for positive control factors (growth factors) to stimulate the cells [201,203]. The SMT may have been originally favoured by researchers because a large number of carcinogens were also found to be mutagens [201]. In addition, tumour-causing viruses were able to transform healthy cells and the subsequent discovery of over 100 oncogenes (gain of function mutations, homologous to human genes) and 30 tumour suppressor genes seemed to be consistent with the SMT [201,203]. Researchers thought they could integrate all these phenomena into one unifying theory [201]. Fifty per cent of carcinogens do not show mutagenicity in the Ames test (*Escherichia coli*) [204,205]. For example, the environmental pollutant TCDD, an extremely potent carcinogen, is not mutagenic [204,206]. A recent review by Soto & Sonnenschein [201] addresses their perceived inconsistencies and difficulties with the SMT.

Conversely, the TOFT is built on the assumption that the default state of cells is proliferative and that carcinogenesis occurs at the tissue level of biological organization. Thus, environmental damage to the tissue milieu in which cells exist may cause them to start dividing again. According to this hypothesis, it is not the cells that are damaged, but there is a disruption of the environment that normally constrains them, which renders them 'malignant' [200].

A point argued by researchers is that cancer cells have many mutations in oncogenes and tumour suppressor genes and some also have chromosomal aberrations. In a review by Prehn [204], the role of mutations in the new cancer paradigm (TOFT) is discussed. Prehn postulates that mutations are not responsible for the neoplasmic phenotype of a cancer cell; rather the mutations are a consequence of the neoplasmic phenotype and not the cause. Prehn's interpretation of the TOFT includes four main premises:

- Cancer is initiated by a loss of gene function.
- DNA repair does not occur or is slow among silenced genes.
- Mutations will eventually 'hard wire' the silenced genes.
- The loss of expression among the genes that suppress developmental genes is seldom caused by mutation.

The main objection to this paradigm is that cancer cells may be clonally derived from a single cell. Prehn argues that the epigenetic adaptive changes will range within a tissue. Prehn states:

> The new paradigm suggests that cancer supposedly originates via adaptive epigenetic changes within a tissue; however, the arisal of focal papillomas suggests that the adaptive changes are not uniformly great among all the cells of that tissue. Thus, some clones may achieve a competitive advantage (based upon epigenetically-induced differential gene expression) and this competitive advantage might eventually and erroneously simulate an origin from a single cell.

A full discussion of Prehn's review is beyond the scope of this text. In an editorial by Soto & Sonnenschein [207], the authors ask the question 'are times a changing in carcinogenesis?'

The TOFT proposes that carcinogens perturb stroma–epithelial interactions, but thus far the actual target of carcinogens has remained hard to pin down. However, Maffini et al. [208] developed a rat mammary tissue recombination model, which encompassed previous attempts to provide a synthetic model that could test both theoretical approaches. The model provided a method for the stroma and epithelium to be exclusively exposed to the known chemical carcinogen *N*-nitrosomethylurea (NMU).

The model involved the surgical removal of mammary epithelium from mammary gland fat pads, and the experimental design would determine the primary target of NMU: either the epithelium or the stroma. Rats were divided into six groups: groups 1–4 had cleared fat pads, groups 5–6 were positive and negative control groups. At 52 days, groups 1 and 2 were exposed to 50 mg kg^{-1} body weight NMU in 0.85 g l^{-1} NaCl solution, groups 3 and 4 were exposed to vehicle (0.85 g l^{-1} NaCl solution). After a period of 5 days, 50,000 mammary epithelium cells were injected into the fat pads. Groups 1 and 4 received cells treated with the vehicle, groups 2 and 3 were injected with NMU-treated cells. The positive control animals were treated with NMU; group 6 animals were treated with vehicle alone to act as a negative control and the control for spontaneous tumours and to show the normal mammary gland architecture.

The results showed that phenotypically normal ducts developed from cultured mammary epithelium cells. Only animal groups that had their stroma exposed to NMU developed neoplasms whether or not the transplanted cells were exposed to NMU; 10 from 13 animals in group 1 and six from eight animals in group 2 developed neoplasmic lesions. There was 100% incidence in the positive control group. The animals that were only exposed to vehicle whether or not the transplanted mammary epithelium cells were exposed to NMU developed no neoplasms. The negative control group (group 5) also developed no neoplasms.

Histopathological examination of the tumours in groups 1, 2 and 5 showed that all the tumours were epithelial in origin. The analysis also showed that the tissue-recombined mammary glands of rats that did not develop neoplasmic lesions, whether or not the cells were NMU treated, appeared similar to a normal rat mammary gland. The authors also challenged the hypothesis that NMU-induced point mutations in codon 12 of the HA-*ras*-1 gene results in carcinogenesis. HA-*ras*-1 gene mutations were not found in all NMU-induced tumours and the mutation was also found in the mammary glands of animals that were not exposed to NMU.

The results of this experiment suggest that in NMU-induced mammary carcinogens, the stroma is the target. In addition, the findings challenge the theory that mammary cancers are initiated by carcinogens that cause mutations in the DNA of epithelial cells. The authors suggest that more research should be directed at the roles of the stroma components and the extracellular matrix in rat mammary carcinogenesis. Also, more efforts should be directed at investigating the role of the stroma in tumour sites other than the mammary gland [208].

Prostate cancer

Prostate cancer incidence

Worldwide prostate cancer is the third most commonly diagnosed cancer. However, in developed countries, prostate cancer is the most common cancer. There is geographical

variation in prostate cancer incidence, with the highest rates found in industrialized developed countries [1,15,209,210]. However, there is also some variation in incidence rates within developed countries [1,211]. The lowest rates are found in Asia, particularly China and Japan [1,212]. In the USA, the incidence rate is approximately 137 per 10^5 $year^{-1}$, whereas in China the incidence rate is approximately 1.9 per 10^5 $year^{-1}$ [213]. In the USA in 2003, an estimated 220,900 men were diagnosed with prostate cancer [214]. In the UK, prostate cancer is the most common malignancy and the incidence has risen consistently year on year [7,215]. The increased incidence rates in one study were described as striking [216]. In the UK, in the 10 years between 1989 and 1997, prostate cancer incidence increased by 38% (see Figure 3) [7]. Figure 9 shows the trend for the number of cases and the age-standardized incidence rate for prostate cancer in England and Wales, 1971–1999 [15]. The incidence trend shown in Figure 9 is mirrored in the rest of the developed world [1].

The marked increases in incidence may in part be due to the diagnosis of latent cancers in men who are asymptomatic, by screening for prostate-specific antigen or from histological examination following prostatectomy operations [1,209,211,217–219]. However, a rising incidence is observed in countries and regions where the effects of screening may not influence the incidence rate [1,210,216]. In addition, in countries where prostate cancer incidence rates have been historically low, increases in incidence rates can now be observed [1]. The analysis of data in some studies suggests that younger people showed a higher rise in incidence than the elderly [208,216,219].

Factors involved in prostate cancer aetiology

The factors involved in prostate cancer aetiology are poorly understood, but genetic susceptibility and environmental factors are thought to play a major role. The risk of

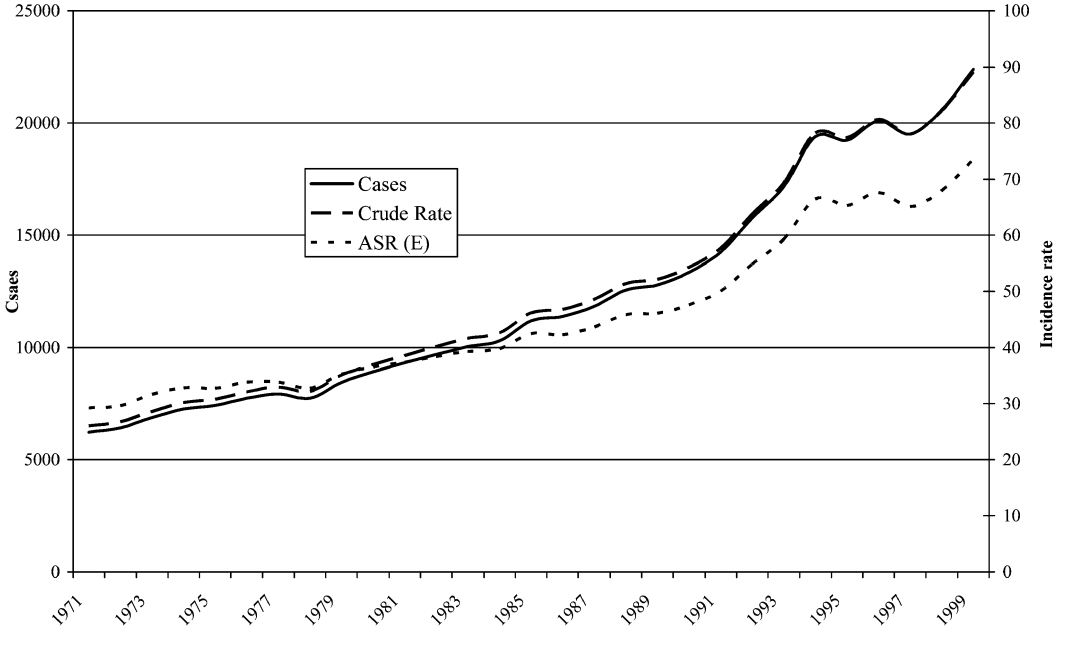

Figure 9. Trend for incidence of prostate cancer in England and Wales, 1971–1999 (all ages). Data taken from [15].

prostate cancer increases two-fold for men with first-degree relatives affected by prostate cancer [209,220]. Mutations in the genes BRCA1 and BRCA2 are associated with an increased risk, but these mutations are rare. Gene linkage studies to find other genes that may be involved in increased risk have been both promising and confusing [220]. Because of the geographical variation in incidence and differences in diet between countries with high and low prostate cancer incidence rates, products such as meat, fish, milk, dairy products and eggs have been postulated in prostate cancer aetiology [1,221–224]. Studies on the correlation of dietary factors and increased prostate cancer risk are conflicting.

A study by Homma and colleagues [221] demonstrated that dietary cholesterol increased oxidative stress and ultimately carcinogenesis in the prostate in rats. In the Netherlands prospective cohort study, no association was found for meat, fish, and diary products (except milk), protein and calcium intake and an increased risk of prostate cancer. However, a positive correlation was found for milk and cured meats, which was in concordance with similar studies [222,225–227]. Li and colleagues [226] demonstrated that the consumption of milk increases the risk of developing prostate cancer in rats and Qin and colleagues [222] put forward the hypothesis that oestrogens in milk may be a factor in the positive correlation between milk consumption and increased prostate cancer risk.

Steroid hormones such as testosterone and oestrogen can induce prostate cancer *in vivo* and *in vitro*. However, circulating androgen and oestrogen levels in epidemiological studies have produced conflicting results. A nested case–control study by Stattin et al. [228] showed no association between high levels of circulating androgens and an increased risk of prostate cancer. A similar result in another nested case–control study was found by Chen et al. [229]. However, Chen et al. postulated that intraprostatic androgen activity may increase the risk of prostate cancer. To obtain more reliable information concerning any possible role of androgens in the aetiology, samples may have to be taken prospectively, preferably at puberty [209].

Environmental contaminants as factors in prostate cancer aetiology

Environmental pollutants with endocrine-disrupting properties have also been postulated as possible factors in prostate cancer aetiology. As discussed in previous sections, pesticides have been shown to have endocrine-disrupting properties. Moreover, studies concerning occupational exposure to pesticides have shown an association with an increased risk of prostate cancer. Data taken from a multisite case–control study in five rural areas in Italy showed that workers involved in agriculture, especially farmers, had an increased risk of prostate cancer. Workers involved in the food, tobacco and chemical industries also showed an increased risk [230]. Farmers were especially vulnerable to organochlorine pesticides. Another study linking occupation and prostate cancer risk by Sharma-Wagner et al. [231] suggested that there is a significant excess risk for men in agriculture-related industries, and for farming in particular there was a significantly elevated risk for prostate cancer. Men working in other industries such as soap and perfume manufacture, and leather processing, had a significantly excess risk of prostate cancer.

A meta-analysis of 22 studies concerning occupational exposure to pesticides and prostate cancer found that the meta-rate ratio estimate of relative risk from 22 studies was 1.13. The increased risk of prostate cancer following occupation exposure, including farmers, was in agreement with three, previously published, meta-rate ratios [23]. A study cohort of 20,025 men who held a licence for pesticide application in Sweden had a significantly increased risk of prostate cancer [232].

A retrospective study by Potti et al. [233] concentrated on the effect of pesticides on aggressive prostate cancer incidence in males younger than 50 years with prostate adenocarcinoma from rural/farming communities in the USA. An exposure index was formulated and a cut-off point of 2400 hours was considered as heavy exposure. The study showed preliminary evidence that pesticide exposure may lead to the early development of prostate cancer and possibly to an aggressive form. The pesticide-exposed patients had a mean survival time of 11.3 months, while unexposed patients had a mean survival of 20.1 months. The authors are now studying the effects of specific pesticide components in PC-3 and LNCaP cells to evaluate for the over-expression of biomarkers such as vascular endothelial growth factor and urokinase plasminogen activator receptor. The authors also concluded that larger epidemiological studies should be carried out to determine which pesticides and pesticide components may be associated with the early progression of aggressive prostate cancer in young ($\leqslant 50$ years) males [233].

Three different *in vitro* and *in vivo* experimental techniques carried out in a study by Ralph et al. [234] showed that HCB weakly agonized androgen action: low levels of HCB enhanced androgen action but high levels suppressed androgen action. PC3 cells transfected with an androgen-responsive reporter gene (firefly luciferase reporter gene) in the presence of a low dose level of HCB (0.5–5 nM) showed increased transcription of the reporter gene. However, high levels of HCB ($>10\,\mu M$) resulted in suppression of the reporter gene. A similar trend was observed for a different prostate cell line (LNCaP) and the use of three different reporter genes (ERE-luc, ARR3-luc, and PSA-luc). Another experiment determined that HCB is not an androgen receptor ligand. A further *in vivo* experiment, in which transgenic mice with a prostate-specific, androgen-responsive promoter upstream of a chloramphenicol acetyl transferase (CAT) reporter gene were prenatally exposed to HCB, showed HCB-modulated androgen action. Following low-dose exposure to HCB in 4-week-old male mice, the proportion of dilated prostate acini, a marker of sexual maturity, was increased, suggesting enhancement of androgen action. In high-dose HCB mice, androgen action was suppressed. In the 8-week-old mice, CAT activity and prostate weight were significantly reduced with medium and high doses of HCB, suggesting the suppression of androgen activity [234].

These latter results concur with a study carried out by vom Saal et al. [121], which also showed that endocrine-disrupting chemicals can exert their effects at environmental exposure levels. They found that low doses of DES (0.02, 0.2 and $2.0\,ng\,g^{-1}\,day^{-1}$) resulted in a significant increase in adult prostate weight and an increase in the number of androgen receptors, when compared with control mice. However, high doses of DES ($200\,ng\,g^{-1}\,day^{-1}$) had the opposite effect: prostate weight was significantly lower than control mice and significantly lower than low-dose treated mice [121].

Tessier & Matsumura [235] have shown that in human prostate cancer cell lines LNCaP and PC-3, erbB-2 kinase, an oncogene that is often over-expressed or amplified in prostate cancer, was activated by the pesticides: β-HCH, o,p'-DDT and heptachlor epoxide (organochlorines), trans-permethrin (insecticide), chlorothalonil (fungicide). o,p'-DDT also causes cellular proliferation of the androgen-dependent LNCaP line. However, no proliferation was observed in the androgen-independent PC-3 line [235]. The proliferation induced by DDT could not be blocked using anti-androgens, indicating that the action of DDT is not via the androgen receptor, a similar finding to a previous experiment with HCB [234,235]. Tessier & Matsumura concluded that their results showed a putative mechanism by which pesticides may be involved in hormonal carcinogenesis [235].

A pilot case–control study by Ritchie et al. [236] investigated the possible relationship between organochlorine pesticides and PCBs with prostate cancer. Levels of 30 PCBs and 18 organochlorine pesticides were measured. The organochlorines dieldrin, p,p'-DDE, trans-nonachlor, oxychlordane, heptachlor epoxide, and PCBs 153 and 180 were detected in at least 20% of all the participants in the study. Oxychlordane and PCB 180 were associated with an increased risk of prostate cancer. The authors concluded that long-term, low-dose exposure to specific organochlorine pesticides and PCBs in the general population may lead to an increased risk of prostate cancer [236]. A study by Alavanja et al. [237] found a significantly elevated risk for prostate cancer in men over 50 years who had occupational exposure to the halogenated fumigant methyl bromide. Exposure to organochlorine pesticides also showed an elevated risk. In addition, other pesticide types showed a significantly increased risk of prostate cancer among pesticide applicators with a family history of prostate cancer but not among pesticide applicators with no family history; suggesting family history–pesticide interactions [237].

The results from a study by Janssens et al. [238] did not find an association with prostate cancer mortality in areas where pesticides were used abundantly, for example, on fruit farms. Fruit production needs the greatest amounts of fungicides, acaricides, insecticides and herbicides, in total up to 25 kg hectare^{-1} year^{-1}. However, higher prostate cancer mortality was found in traditional potato growing areas. The authors suggested that this may be due to a long-standing effect of pesticides now currently banned, such as DDT [238].

The studies discussed above suggest that occupational exposure to organochlorines is an important factor in the aetiology of prostate cancer. In addition, the evidence provided by *in vitro* studies suggests that exposure to environmentally relevant levels of specific organochlorines and endocrine-disrupting chemicals could be a major factor in increasing prostate cancer incidence.

Testicular cancer

Testicular cancer incidence

Testicular cancer is the most common malignancy in 20–34-year-old men, and is increasing in incidence worldwide. The majority of this increase is in developed industrialized countries, i.e. North America, Europe, Oceania and Japan [239]. However, Denmark has reported a decrease in incidence [150,240]. The worldwide rate of testicular cancer has doubled in the last 40 years. There seem to be geographical differences in the incidence of testicular cancer; ethnicity also plays a role in the differences in incidence observed between different countries and within differing regions of countries [239,241]. This suggests that environmental influences could be involved in the aetiology. However, the differences in incidence observed between differing ethnic groups suggest that genetics is also involved in testicular cancer aetiology. In the UK, the familial risk accounts for approximately 2% of the overall incidence. A mutation in chromosome Xq27 has been found to be associated with the familial risk. Brothers of affected men have a six to 10 times risk of developing testicular cancer [242].

In the UK, 80% of testicular cancer incidence affects men aged under 45 years. Considering 10-year age groups, testicular cancer has increased in all age groups from 20 to 59 years but not in the over 60s. Overall, incidence was 5.4 per 10^5 in 1997 compared with 2.9 per 10^5 in 1971 [15]. A study by dos-Santos Silva and colleagues [243] compared

incidence rates in children and young adults in England and Wales. The incidence rate overall rose by 3.4% between 1965 and 1990. The incidence rate in under 15 year olds rose by 1.3% from 1962 to 1995. This rise in incidence in under 15 year olds was paralleled by a rise in young adults. Both trends are in the same direction, suggesting a common aetiology, possibly prenatal [237]. Figure 10 shows the trend for the incidence of testicular cancer for England and Wales (all ages), 1971–1999 [15].

Occupational exposure to polychlorinated compounds has been shown to increase the risk for some cancers. Hardell et al. [244] examined occupation histories in a case–control study in Sweden and found a high risk of testicular cancer in people exposed to PVC; exposure to other types of plastics did not increase the risk. However, a further case–control study was carried out by Hardell et al. [245] and no association between PVC exposure and testicular cancer was found.

The average age of testicular cancer incidence is 25–30 years, suggesting that the exposure to carcinogens was in early life or even *in utero*. Pre-malignant germ cells that eventually give rise to testicular cancer are thought to originate during foetal life [150]. Swerdlow and colleagues [246] carried out a study on risk factors for testicular cancer in a case–control study in twins. They found an increased risk of testicular cancer in twins with longer limbs than their co-twin. A correlation between height and testicular cancer has also been observed in another study conducted by Rasmussen et al. [247]. The authors of these studies concluded that nutritional factors that affect growth before puberty may cause testicular cancer. The study by Swerdlow et al. [246] also reported an increased incidence of testicular cancer among twins with cryptorchidism.

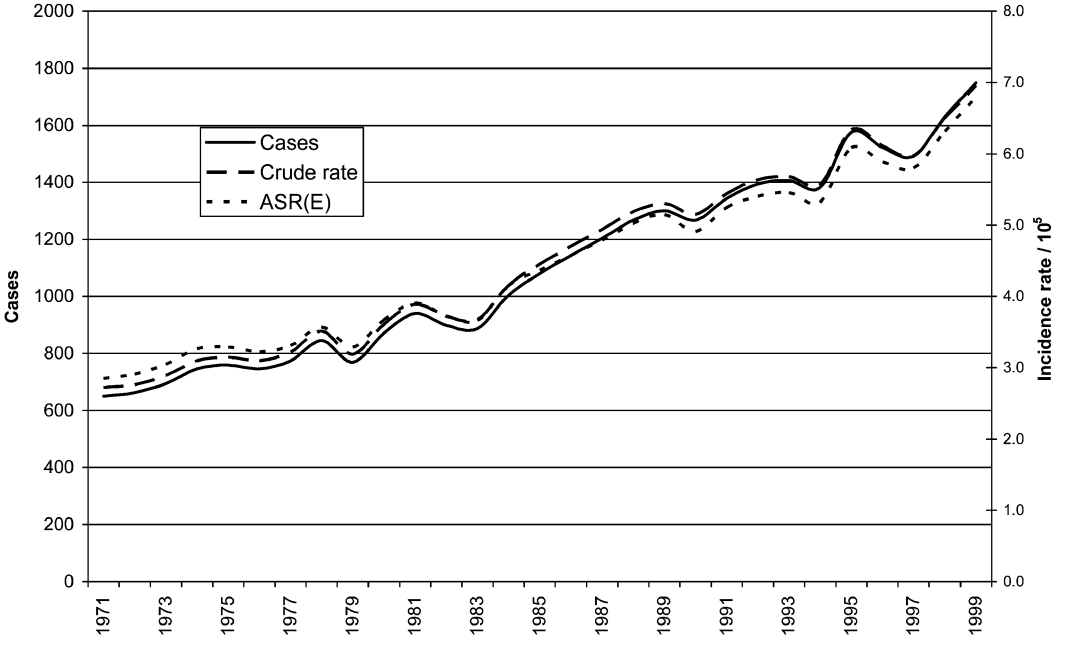

Figure 10. Trend for incidence of testicular cancer in England and Wales, 1971–1999 (all ages). Data taken from [15].

Early life exposure to carcinogens and testicular cancer

There is a growing body of evidence to suggest that exposure to increased oestrogen levels in the prenatal period may be involved in the aetiology of cancer. In 1971, a now well-cited study by Herbst et al. [248] demonstrated that women given the potent oestrogen DES to prevent spontaneous abortion gave birth to female offspring who went on to develop clear cell adenoma of the vagina. If testicular cancer is considered: increased exposure to maternal oestrogen levels has been shown to be associated with testicular cancer [249,250]. Counter-intuitively, one study found that mothers smoking 12 cigarettes a day decreased the risk of testicular cancer. In addition, the disorders cryptorchidism, testicular cancer, low sperm count and hypospadias may be a syndrome of disorders known as TDS, which have a common aetiology during foetal life and may be a consequence of increased oestrogen exposure [82,150,251,252]. Each of these disorders is a factor for any of the other disorders in the syndrome. Therefore, a factor implicated in the aetiology of one of these disorders is also a factor in the aetiology of one of the other disorders.

The 'oestrogen hypothesis'

A review by Sharpe [150], which examined data pertinent to his 'oestrogen hypothesis', cites a case–control study by Dieckmann et al. [253] that failed to find any evidence to back up the hypothesis that maternal exposure to excess exogenous oestrogen in males was a risk factor for germ cell cancers. Stroshnitter et al. [249] examined DES exposure *in utero* and after the first 16 years of follow-up obtained an uncertain result with respect to testicular cancer, but they concluded that for males, DES exposure *in utero* is not a factor in the aetiology of other cancers. Men exposed to DES *in utero* did have an increased relative risk of testicular cancer compared with controls, but the authors could not rule out a chance finding. However, Weir et al. [250] found an elevated risk between exogenous oestrogen exposure *in utero* and testicular cancer.

Oestrogens may induce male reproductive disorders, including testicular cancer, via many different mechanisms, for example, androgen suppression. Sharpe [150] cites a study by Haavisto et al. [114] in which potent oestrogens such as DES suppress androgen production in foetal rats, and a study by Williams et al. [115] that showed that DES and ethinyl oestradiol exposure leads to reduced testosterone levels in neonatal rats. However, the same study showed that exposure to low potency environmental oestrogens, octylphenol and bisphenol A, did not produce the same results. DES suppresses Leydig cell function, which results in a significant reduction in testosterone levels in foetal testis and blood, which is dose dependent. Williams et al. [115] demonstrated that treatment with high, but not low, doses of potent oestrogens such as DES and ethinyl oestradiol induces widespread structural and cellular abnormalities of the testis and reproductive tract before puberty. Haavisto et al. [114] also showed that DES doses of $100\,\mu g\,kg^{-1}\,day^{-1}$ administered to pregnant rats resulted in the suppression of testosterone in the testis by as much as 70%. Sharpe points out that similar doses of DES were given to pregnant women between 1950 and 1970 [115]. Haavisto et al. [114] also showed that dioxin causes dose-dependent suppression of foetal testosterone.

Could exposure to environmental pollutants with oestrogenic activity increase the risk of TDS and testicular cancer? Hardell & Eriksson [254] carried out a case–control study in which they examined levels of the sum of 38 PCBs, DDE, HCB and chlordane, in cases with testicular cancer and age-matched controls. In addition, the mothers of cases and controls were also examined. The results showed that only one type of chlordane,

cis-nonachlordane, was significantly raised in cases. However, compared with control mothers, the mothers of cases were found to have significantly raised levels of total PCBs, HCB, cis-nonachlordane, and the sum of chlordanes. The authors pointed out that persistent organic pollutant levels are decreasing in the population and the highest concentrations were found in the early 1970s. The median age of the cases was 30 years. Therefore, most of them were born during the period with high concentration in the population [254].

Environmentally relevant levels of xenoestrogens and testicular cancer

Sharpe addresses environmental oestrogens as factors in the aetiology of testicular cancer. Most environmental xenoestrogens, when assayed for oestrogenic activity, are thought to be weak. He concludes that the weak oestrogenic activity of most environmental oestrogens is probably not important in cancer aetiology [150]. However, as discussed earlier, there are studies that show endocrine disruption and *in utero* effect with substances at low levels and low oestrogenicity. Hormones involved in organogenesis act at part per trillion levels and hormone-disrupting chemicals are found in similar serum concentrations [65].

A good example of a study showing the effect of environmentally relevant levels of bisphenol A on CD-1 mice was carried out by Markey and colleagues [199]. Although the study examined the effect of bisphenol A on developing mammary tissue and not the developing male reproductive tract, the study produced evidence of adverse effects from oestrogen exposure at background environmental levels. Bisphenol A is an environmental oestrogen used in the manufacture of polycarbonate plastics and epoxy resins, which are used in the production of infants' milk bottles, reusable food containers and the interior coating of food tin cans and many other widely used products. The study demonstrated that *in utero* exposure to environmentally relevant levels of bisphenol A results in perturbed mammary tissue development. The exposed mice had increased terminal ducts and terminal end buds when compared with controls, which predispose the mice to mammary gland cancers later in their adult life [199]. The CD-1 mice were used because they have intrinsic oestrogen resistance.

The major endocrine disrupter Vinclozolin (fungicide) has been shown to have an *in utero* effect resulting in maldescent of the testis in neonatal rats [113]. In addition, the phthalate ester, mono-n-butyl phthalate (MBP) has a dose-dependent effect on *in utero* and postnatal testis descent in rats. High doses of MBP (1.0 and $0.5\,g\,kg^{-1}\,day^{-1}$) inhibit the transabdominal descent of the testis, which the authors concluded is due to the oestrogenic activity of MBP. However, low doses of MBP ($0.25\,g\,kg^{-1}\,day^{-1}$) inhibit inguinoscrotal testicular descent in postnatal rats, which may be due to the anti-androgen affect of MBP at low doses [96].

There are conflicting studies regarding the effects of xenoestrogens with low oestrogenic activity on animals, but if these compounds are not directly involved in the aetiology of testicular cancer, there is growing evidence that they may be indirectly involved. High levels of endogenous oestrogen are a known cause of testicular cancer [241]. If high levels of endogenous oestrogens cross the placenta, adverse effects on the foetus may be observed. The enzyme oestrogen sulphotransferase (SULTE1E1) is responsible for the inactivation and excretion of oestradiol. However, if this enzyme is inactivated, increased levels of oestrogen can reach the foetus. Low levels of PCBs have been shown to suppress SULTE1E1 activity. Hydroxylated PCBs inhibit the enzyme and the level of inhibition depends on where the hydroxyl substations are on the phenyl ring. Some congeners of PCBs have a greater affinity for SULTE1E1 than its natural substrate. A PCB congener

found to be one of the most potent inhibitors of SULTE1E1 is also found to be one of the most abundant in the blood and tissues of humans and animals. Inhibition of this enzyme may increase local levels of oestrogen in oestrogen-sensitive tissues, for example the testis and mammary glands [101]. Further studies by Kester et al. [100] revealed that other organochlorines, in addition to PCBs-OH, also have a potent inhibitory effect at very low levels. The concentrations causing 50% inhibition (IC_{50} values) were in the low or even subnanomolar range. The potent inhibitors 2-hydroxy-3,7,8-trichlorodibenzo-p-dioxin, 2-hydroxy-1,3,7,8-tetrachlorodibenzo-p-dioxin, 3-hydroxy-2,4,7,8-tetrachlorodibenzofuran, and 3-hydroxy-2,4,7,8,9-pentachlorodibenzofuran, with IC_{50} values of 34, 4.1, 1.4 and 0.18 nm, respectively, have been identified in mammals [100].

Environmental influences in childhood cancer aetiology

Childhood cancer incidence and common childhood tumour sites

A report released in 2003 by the US Environmental Protection Agency shows increasing childhood cancer incidence [64]. Cancer in childhood is quite rare when compared with adults. However, in the USA, only accidents and injuries cause more deaths in children between 1 and 19 years of age (see Figure 11) [64]. Similar trends for childhood cancer can be observed in the UK and the rest of the developing world [12,13,64,255] (see Figure 12a).

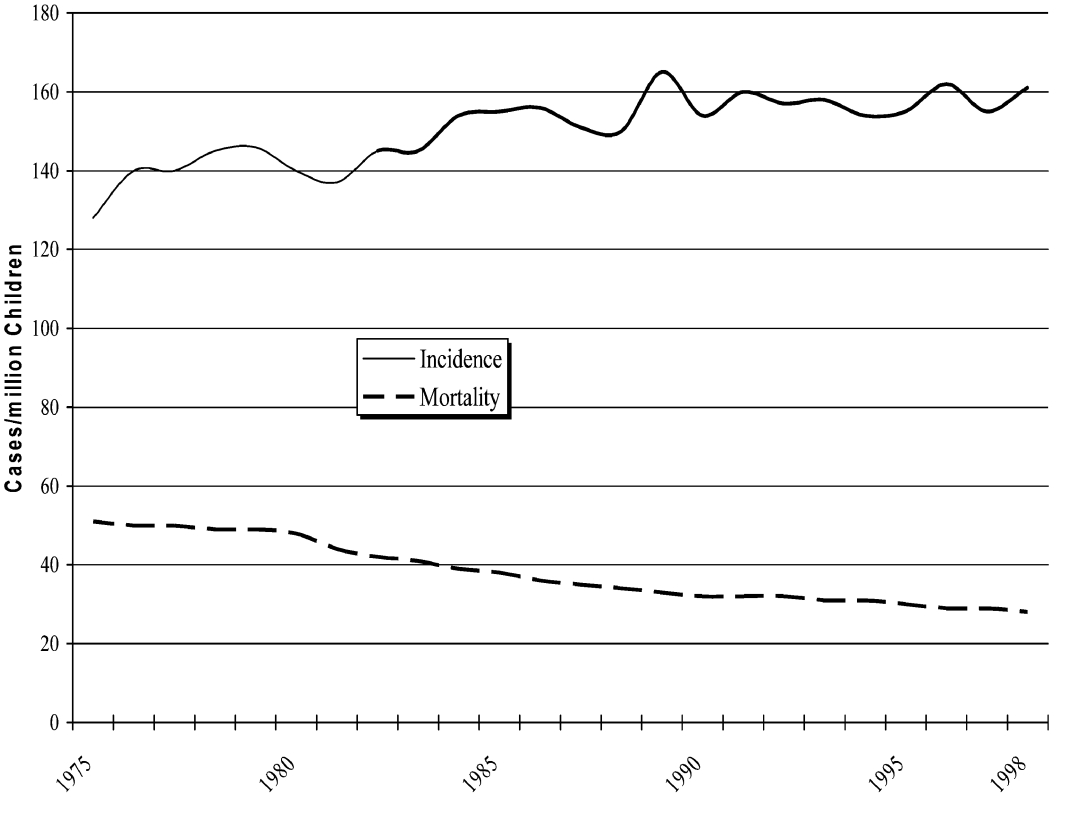

Figure 11. Cancer incidence and mortality trends for children under 20 years in the USA (1974–1998). Data taken from [64].

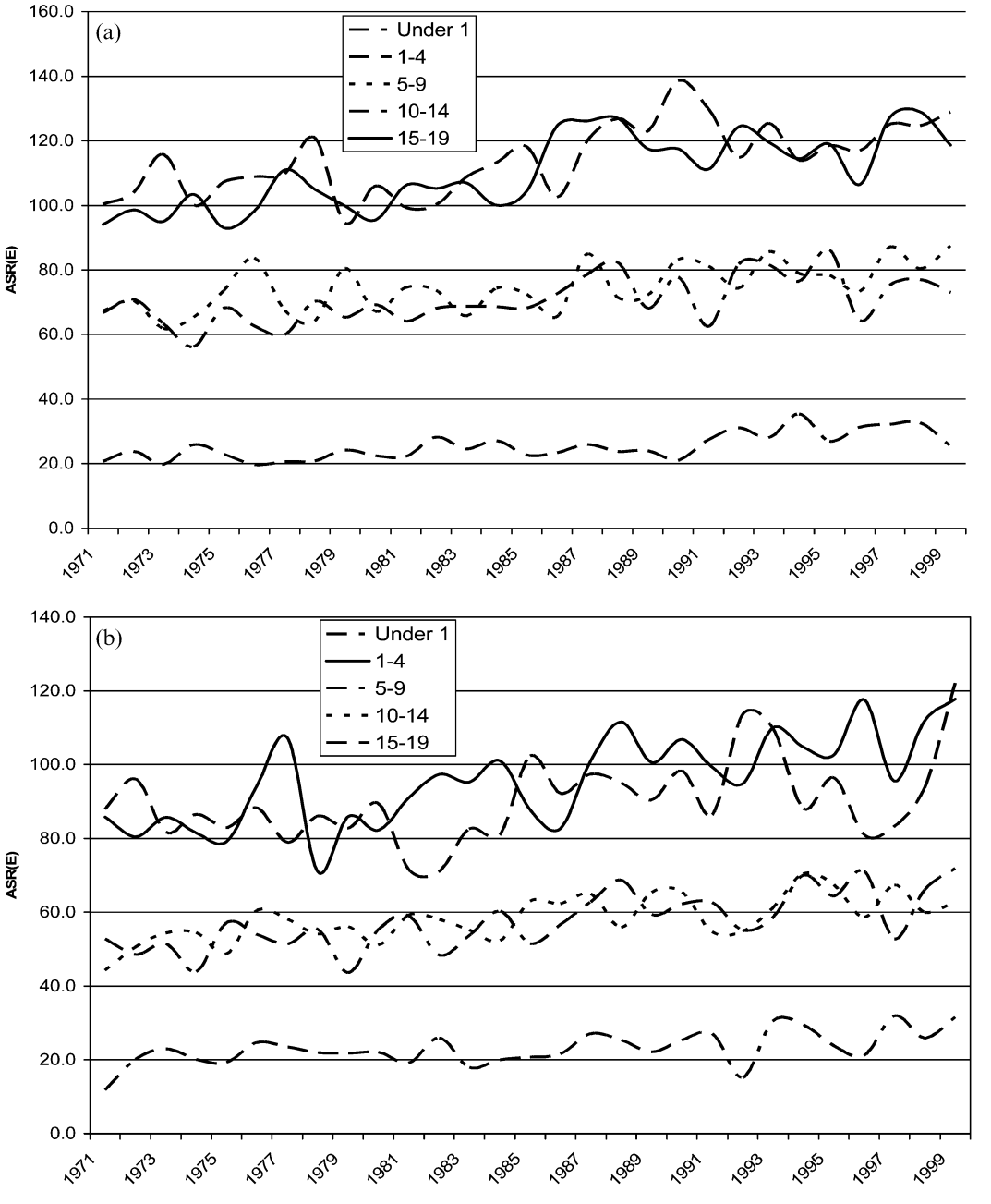

Figure 12. Trend for age-standardized incidence rate (European) for all malignancies in children under 20 years in England and Wales, 1971–1999, for (a) males and (b) females. Data taken from [64].

In the USA, the childhood cancer incidence rate for all cancer sites has increased from 128 cases per 10^6 in 1975 to 161 cases per 10^6 children in 1998 (see Figure 11) [64]. However, the mortality rate is decreasing: the mortality rate has fallen from 51 deaths to 28 deaths per 10^6 children. If specific cancer sites are considered, the incidence rates of acute lymphoblastic leukaemia, central nervous system cancer, NHL, thyroid cancer, malignant

melanoma, germ cell tumours, soft tissue carcinomas, malignant bone tumours, neuroblastomas, Wilms' tumours and hepatoblastomas have increased. However, from available data, only acute myeloid leukaemia and Hodgkin's lymphoma have had decreased incidence rates since 1975 [64].

In the UK, the six most common childhood cancers are: leukaemia, brain and spinal cord cancers, lymphomas, neuroblastomas and renal cancer. However, there is also a marked upward trend in the incidence of testicular cancer in children [13]. Figure 12a, b shows the increasing trend for the age-standardized incidence rate for childhood cancer (all malignancies) in England and Wales [15]. Cancer incidence in children in North West England is rising and the increase is real; it is not a consequence of improved diagnosis or reporting [14]. A recent analysis of cancer incidence data for England shows that the overall incidence among teenagers, adolescents and young adults is rising. The biggest increase is among 20–24 year olds, predominantly in lymphoma, melanoma and germ cell tumours, including testicular germ cell tumours. Cancer is the leading cause of death apart from accidents in England among 13–24 year olds. Between 1979 and 2000 the overall rate of cancer incidence in 13–24 year olds rose from 15.4 to 19.8 per 10^5; a total increase of 29% and an average increase of 1.2% year^{-1} [256,257].

- Leukaemia accounts for around 33% of all childhood cancers; acute lymphoblastic leukaemia is the main form in children; around four out of five leukaemia cases in children is acute lymphoblastic leukaemia. Leukaemia in children occurs mainly at 2–3 years of age.
- Brain and spinal cord malignancies are the most common form of solid tumours in children. In England and Wales they are responsible for 25% of childhood cancers. Between 30 and 50% of childhood malignant brain tumours are astrocytomas. Childhood brain and spinal cancer incidence rose from 19 cases per 10^6 in 1971 to 26 cases per 10^6 in 1994, which was an increase of approximately 40%. Since 1971, the incidence rate has doubled in the 5–9 years age group.
- Lymphomas occur more frequently in older children aged 10–14 years.
- Soft tissue sarcomas are responsible for approximately 7% of malignant neoplasms in children. They are the fourth most common form of childhood cancer in England and Wales. The most common form in children is rhabdomyosarcoma.
- Neuroblastomas are embryonal tumours, which account for approximately 6% of cancers diagnosed in children in England and Wales. Three-quarters of cases occur in children aged under 4 years.
- The majority of renal cancers are Wilms' tumours (nephroblastoma). They are most commonly diagnosed in children between the ages of 1 and 3 years [83,256].

Environmental factors involved in childhood cancer aetiology

Ionizing radiation is an established risk factor for childhood cancer, and leukaemia clusters around nuclear power stations have been investigated. Leukaemia clusters around the Sellafield reprocessing plant in the UK were investigated following public concern. Ionizing radiation was not thought by some to be the cause of the increased incidence in leukaemia. An infectious agent was postulated by Doll [58] as being responsible. Doll hypothesized that the infectious agent was brought into the local community by population mixing. The hypothesis of population mixing is based around the introduction of a wide variety of infectious agents into a previously unexposed, sparsely, populated area. Rapid population

influx into a rural area such as Sellafield, particularly by workers from urban backgrounds across the North West of England who may have been exposed to many infectious agents, was proposed by Doll to have caused the leukaemia cluster. There was a similar finding for a cluster around the nuclear power plant in La Hague, France [258]. Nonetheless, the viral aetiology hypothesis remains controversial.

Cancer treatments in childhood, for example, chemotherapeutic agents, can be risk factors for re-occurrences of primary tumours at different sites later in life [83]. A study suggesting that breast-feeding may offer protection against childhood cancer, especially acute lymphocytic leukaemia [169], has been challenged by Lancashire & Sorahan, who concluded that there is no evidence to support the protective hypothesis [259].

It is difficult to find a specific causal link between environmental pollutant exposure and cancer development. Many factors may be involved in the aetiology of childhood cancers. As discussed above, population mixing and infectious agents have been hypothesized for leukaemias and some brain tumours [58,61,258,260,261]. Space–time clustering acute lymphoblastic leukaemia incidence analyses by McNally et al. [262] suggested that an *in utero* infection may be a factor in acute lymphoblastic leukaemia aetiology.

Environmental exposure to persistent organic pollutants such as PCBs, pesticides and other endocrine disrupters, has been studied to a lesser extent in the case of children and more epidemiological studies are needed [83]. Childhood behaviour puts children at risk to high exposures: they crawl on the ground, they put their fingers in their mouths, and they inhale more air per unit body weight than adults. Children are potentially at risk of exposure to more than 85,000 synthetic chemical compounds, most of which have been developed since World War II [64].

Exposure to PCBs early in childhood has been shown to have neurological and immunological effects on children. A study on pre-school Dutch children suggested that perinatal exposure to PCBs and dioxin, probably from lactation, persists into childhood and has an adverse effect on infection susceptibility. Weisglas-Kuperus et al. [263] found that the effects of perinatal exposure on the immune system led to increased middle ear infections and other infectious diseases. Paradoxically, perinatal PCB exposure led to a decrease in allergy in this study and a study by ten-Tusscher et al. [264] that also found that perinatal background dioxin exposure led to persistently decreased thrombocytes, increased thrombopoietin, and increased CD4+ T-helper and increased CD45RA+ cell counts. In a recent review, human prenatal exposure to PCBs and their effect on neurodevelopment was studied. The authors found that the neonates had impaired reflexes and at 4 years of age deficits in cognitive skills were observed [265].

Could pesticide exposure be implicated in childhood cancer aetiology? A study by Rodvall et al. [22] in Sweden examined the cancer risk in offspring of male pesticide applicators in agriculture. The authors found no link to childhood cancer. A similar study in the USA and Canada also came to the conclusion that parental pesticide exposure was not an important factor in the aetiology of childhood brain cancers [266]. A study examining the critical windows of exposure of household pesticides, and the subsequent risk of childhood leukaemia conducted by Ma et al. [267], suggested that exposure to these substances increased the risk of childhood leukaemia. The risk of childhood leukaemia was determined by the period (pregnancy, year 1, year 2, and year 3) when exposure occurred. The highest risk was during pregnancy and the lowest was at year 3. The risk of leukaemia was associated with indoor pesticides but not outdoor household pesticides [267].

The study by Ma et al. [267] showed that exposure to pesticides during pregnancy and the first year of life had the principal adverse affect. Pre- and perinatal exposure to

environmental pollutants is obviously an important factor in the aetiology of perturbed development. Could prenatal or perinatal exposure to pesticides and other endocrine-disrupting chemicals lead to cancer development in childhood?

Pre- and perinatal exposure to environmental carcinogens

The intrauterine environment is exquisitely sensitive to ambient hormone level fluctuations

Evidence suggests that developing children are vulnerable to environmental exposures, from conception to adolescence. Exposures to ionizing radiation and DES *in utero* are undisputed environmental factors involved in the aetiology of cancer [66,248,265,267–269]. There are critical sensitive periods during organogenesis and environmental exposure to chemicals may have differing or no adverse effects on a developing foetus, depending on the precise time of exposure. A specific developmental process occurs during a specific period of time. Thus, a chemical may have an adverse effect at one point in time, but before or after that point in time the chemical may have no effects at all [270–272].

The intrauterine environment has been shown to be exquisitely sensitive to ambient hormone fluctuations at a few parts per trillion; this is approximately the same concentration that dioxins and other organochlorines are found in serum. In a classic study involving incubating mice pups, differences of only 30 ppt in the ambient uterine level of oestrogens between the pups had effects on their subsequent behaviour as adults. Females incubated between two males were more aggressive than their sisters [273]. A study investigating *in utero* exposure to PCBs from eating fish from Lake Michigan, USA, found that prenatal exposure to PCBs was associated with lower full-scale and verbal IQ scores. In addition, children with the highest PCB exposures were three times as likely to have low average IQ scores and twice as likely to be 2 years behind in reading comprehension. These results suggested that the developing foetal brain is extremely sensitive to PCBs. The authors of the study concluded that *in utero* exposure to PCBs in concentrations that are slightly higher than the general population can result in long-term consequences for intellectual function [274].

The high rates of cell proliferation and differentiation render the developing child's cells susceptible to mutagenic and epigenetic alteration. The blood–brain barrier and the placenta act as barriers to potentially harmful substances. However, in the developing foetus, these protective barriers are not fully developed and can allow harmful substances to reach sensitive developing organs such as the brain [268,270]. *In utero* DNA damage resulting from environmental pollution has been shown to be associated with somatic gene mutation in newborns. The authors of this report state that their results provide a molecular link between transplacental exposure to pollutants and somatic mutation [66].

Animal models of prenatal exposure to endocrine disrupters and carcinogenesis

Human epidemiological and biological data are inconsistent, but the animal evidence of prenatal exposure to environmental carcinogens is abundant and has been reviewed extensively [82,106,116,268,271,275]. A review by Birnbaun & Fenton [275] concerning cancer and developmental exposure to endocrine disrupters explores suggested links in human and animal models. The authors cite studies in which links have been found between occupational prenatal exposure and, in some cases, preconceptional paternal exposures and cancer for hydrocarbons [276], solvents and paints [277], pesticides [278,279] and parental smoking [280].

Animal studies have suggested that *in utero* exposure to natural and synthetic oestrogens is associated with breast and vaginal cancers, and this association has also been demonstrated in humans [196,248,281]. There is some preliminary evidence that women exposed to DES *in utero* may have an increased risk of developing breast cancer later in life. The results of a cohort study showed an association between DES exposure *in utero* and an increased risk of breast cancer. The results were not statistically significant, but as the cohort was of mean age 43 years, the authors will be conducting a further follow-up [196].

As discussed in detail earlier, rodent studies have suggested that exposure to dioxin and other organochlorines *in utero* may predispose female offspring to breast cancer, as demonstrated by Brown and colleagues [197] and Fenton et al. [198] for TCDD, and Markey et al. [199] for bisphenol A.

A study by Emmen et al. [282] investigated whether inactivation of the insulin-like factor 3 gene (Insl3) by *in utero* DES exposure would result in cryptorchidism in male mice. Insl3 plays a role in transabdominal testicular descent, which involves the development of the gubernaculum. Histological examination of the mouse embryos showed differences in the position of the testis between treated and control mice. In treated mice the testes were always in a higher abdominal position than in the control mice. In addition, DES-treated mice showed an undifferentiated female-like gubernaculum. Further RNA analysis showed a 70% decrease in Insl3 mRNA compared with control mice. The Insl3 gene has been characterized in humans and *in situ* hybridization has shown Insl3 to be exclusively expressed in Leydig cells [282]. This study demonstrated the possible mechanism by which DES exposure *in utero* causes cryptorchidism. As discussed in a previous section, cryptorchidism is a factor in the aetiology of testicular cancer.

The hypothesis that early life exposure to environmental factors such as organochlorine endocrine disrupters may be involved in cancer aetiology is plausible. There is, however, a study that disagrees with this hypothesis. Hsieh et al. [283] reason that populations with high pregnancy oestrogen levels should have increased rates of testicular cancer. The study examined pregnancy oestrogen levels in two populations (Boston, USA and Shanghai, China) with different testicular cancer rates. Women in Boston had lower oestrogen levels than the women in Shanghai, but the testicular cancer rate was higher in Boston than Shanghai.

Data obtained from animal studies concerning environmental exposures *in utero* and the subsequent development of cancer are extensive. However, animal evidence must be treated with caution because results from animal experiments are not automatically applicable to humans. An example is prenatal rat exposure to saccharin, which is an artificial sweetener. Prenatal exposure results in an increased incidence rate of bladder cancer when compared with adult rat exposure. However, following a comprehensive review of studies regarding saccharin exposure to rats, mice, hamsters and humans, saccharin was considered to be safe [281,284,285].

Reduction in female body burden of organochlorines: implications for the foetus and infant; placental and lactation transfer of organochlorines to foetus and infant

Although organochlorines such as dioxins and PCBs bioaccumulate in adipose tissue, females can reduce their body burden transplacently and via lactation [130,133,135]. It has recently been shown that HCB also exhibits transplacental transfer [132]. The foetus gets a huge dose compared with the dose that adults receive from background levels. Consequently, most testing on adult animals may not give results that apply to the foetus and infant. One study indicated that the body burden of organochlorines in women can

potentially reduce by as much as 69% over a 30 month period. Dioxins, dibenzofurans, PCBs, DDE, and HCB were measured in blood and milk samples. Dioxin levels in the milk samples fell from 309 to 173 ppt and dibenzofuran levels fell from 21 to 9 ppt. The authors calculated that the mother's body burden of dioxin reduced from 310 to 96 ng dioxin toxic equivalents, approximately 69%. It was calculated that the twins born to the mother received the equivalent of 115 ng dioxin each from breast-feeding [135]. A study on urban foxes demonstrated similar results to the study above. The authors concluded that urban foxes possess the requirements to enable assessment of the toxic health hazards in the local environment [286].

A study on school-aged children (7 years) suggested that those who were breast-fed had a higher body burden of organochlorines than those who were bottle-fed. The study found a strong dose-dependent relationship between the length of time the infants were breast-fed and the concentration of all the organochlorines measured (DDE, HCB, β-HCH, and the sum of PCBs including the congeners 101, 118, 138, 153, 170, 180, 183, and 187). There was a doubling of organochlorine whole blood concentration in children who were breast-fed for a period greater than 12 weeks compared with bottle-fed children [133]. However, another study revealed that prenatal uptake of PCBs and HCB has declined by 75 and 95%, respectively, over the last 15 years [287].

In utero *exposure to PCBs and HCB from tobacco smoke*

The PCB and HCB burden is significantly increased in human neonates with parents who smoke, when compared with passive smoking mothers and non-smoking families. In addition, a transplacental tobacco carcinogen (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone) has been found in the urine of neonates. PCBs and HCB have been shown to have a co-carcinogenic effect with 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone in mice [288]. The uptake of PCBs and HCB by neonates from tobacco smoke with 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone could be a risk factor for childhood cancers and the authors concluded that further studies are required to investigate the possible risks associated with parental smoking, with special consideration of the tumour-promoting properties of PCB and HCB [289].

Immune system cancers

Characteristics of immune system cancers

Cancers of the immune system include lymphomas, leukaemias and multiple myeloma. Lymphomas typically arise from lymphoid tissue and comprise two major groups: Hodgkin's lymphoma and NHL. NHL is a collection of malignancies and Hodgkin's lymphoma is distinguished from NHL by the presence of large malignant cells called Reed–Sternberg cells. Leukaemias are tumours arising from a group of white blood cell types called leukocytes. Multiple myeloma, which is the least common of the immune cancers, is a malignancy of the plasma cell characterized by migration and localization to the bone marrow.

NHL and multiple myeloma incidence

NHL has increased rapidly in the majority of developed countries over the past few decades. The highest incidence rates for NHL are found in the USA and Australia for both

males and females. The lowest incidence of NHL is found in India and China (see Figure 13a, b) [256]. The incidence rate of NHL has started to fall in the USA, Sweden, Finland and Denmark, but not in Norway or the UK [15,254]. A possible reason for this

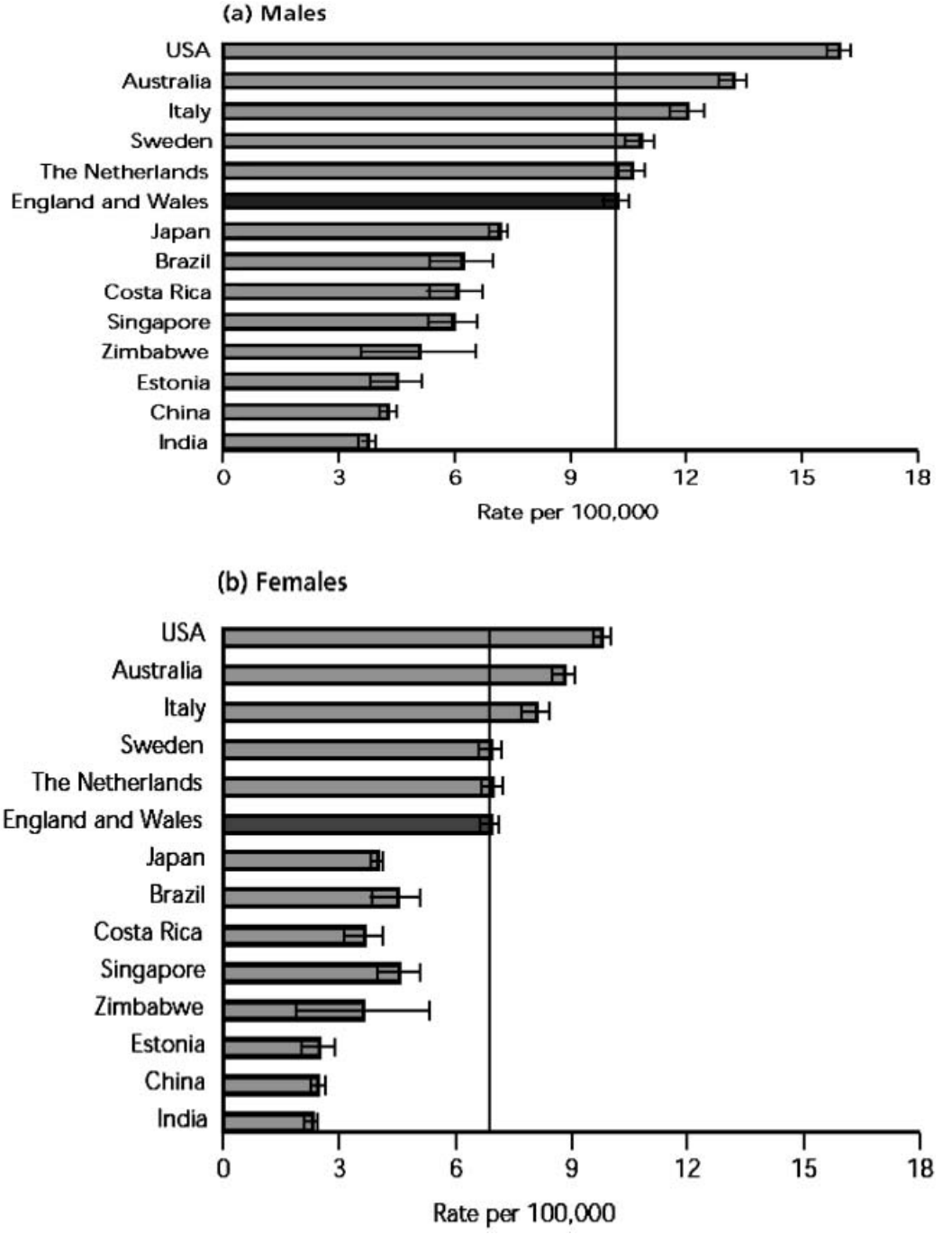

Figure 13. International age-standardized incidence for (a) males and (b) females. Adapted from [253] (Permission for use granted by Crown Copyright).

decline is discussed in detail below. Multiple myeloma is also increasing and childhood leukaemias also show increasing incidence in the USA [64] and the UK [256]. Figure 14 shows the trend for the incidence of NHL in England and Wales, 1971–1999 [15]. The incidence rate of NHL in England and Wales is comparable to the rest of Western Europe [256].

Environmental factors involved in NHL aetiology, particularly pesticides, dioxins and dibenzofurans

The factors involved in the aetiology of NHL include HIV and Epstein–Barr virus (EBV) infection, immunosuppression by drugs (e.g. cyclosporin A), family history, immunodeficiency disorders, and occupational exposure to chemicals, particularly pesticides [51,69,70,256,290–297]. EBV is a human herpes virus and infection with the virus is a major risk factor for NHL in Africa and other developing countries. The virus is associated with Burkitt's lymphoma (a subgroup of NHL) and lymphomas arising from severe immunosuppression. Table II shows organochlorines that have been shown to cause immune cancers in laboratory animals [298].

Occupational exposure to pesticides has been shown to increase the risk of NHL, particularly among farmers, pesticide applicators and other agricultural workers. In the Agricultural Health Study, pesticide exposure (alachlor) for applicators in Iowa and North Carolina, USA, was found to be associated with an increased risk for all lymphohaematopoietic cancers among applicators, although the risk for NHL was significantly lower than expected. There was a significant increasing trend associated with lifetime exposure-days and intensity-weighted exposure-days. In the highest exposure category, a marked increasing risk was found for leukaemia and multiple myeloma [20].

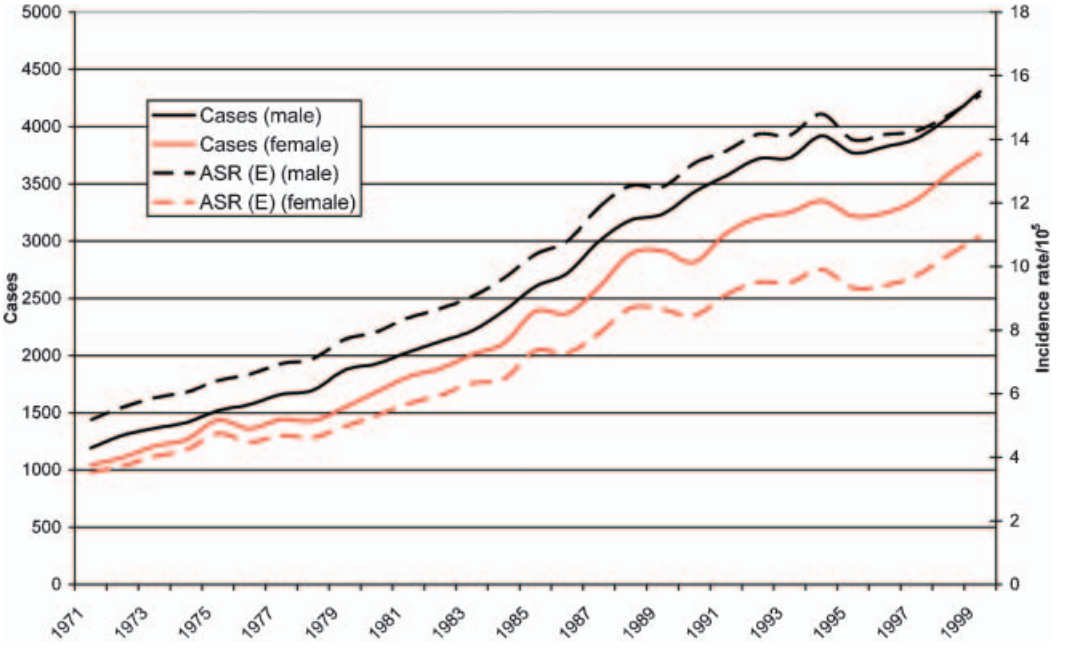

Figure 14. Trend for incidence of non-Hodgkin's lymphoma (C82-85) in England and Wales, 1971–1999 (all ages). Data taken from [15].

Table II. Organochlorines that have been shown to cause immune cancers in laboratory animals. Adapted from [298]. Pandora's Poison, by Jo Thornton (ISBN 0–262–20124–0), The MIT Press, (permission granted for use by The MIT Press).

Lymphomas	Leukaemia
Atrazine	Atrazine
Chlorinated paraffins	1,1-Dichloroethylene
Dichloroacetylene	Dichloromethane
1,2-Dichloroethane	Dichlorvos
2,6-Dichlorobenzonitrile	3,3`-Dimethylbenzidine dihydrochloride
4,4′-Methylenedianiline dihydrochloride	4-Hydroxaminoquinoline-1-oxide hydrochloride
Nitrogen mustard hydrochloride	Mirex
Nitrogen mustard N-oxide	Tetrachloroethylene
2,4,6-Trichlorophenol	2,4,6-Trichlorophenol
2,3,7,8-TCDD	Tris(chloroethyl)phosphate
Uracil mustard	

TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin.

In Nebraska, USA, which is a rural, agricultural area, the incidence of an aggressive subtype of NHL has increased two-fold. A population-based case–control study was carried out to investigate any possible association between agricultural exposure and increased risk of NHL. The results showed that an increased risk of 50% was found with 2,4-dichlorophenoxy-acetic acid (2,4-D). In addition, personal exposure to 2,4-D above 20 days year^{-1} was associated with a three-fold risk. Organophosphate, carbamate and chlorinated hydrocarbon insecticides were also associated with an increased risk. The study also examined the incidence of NHL in areas where ground water was contaminated with the pesticide Atrazine and nitrates from fertilizers. In areas of intense fertilizer use and where more than 20% of wells were contaminated by nitrate, NHL incidence increased two-fold [70]. These findings were confirmed in a study by Ward et al. [69]: long-term nitrate exposure from drinking water in rural areas was associated with an increased risk.

In another case–control study in Nebraska, Zahm et al. [297] investigated the risk of NHL in women who had been exposed to pesticides. The results showed that no risk was found for women who lived on farms, even if pesticides were used on the farm, but only a small number of women were recorded as actually mixing or spraying the pesticides. However, women who used organophosphate insecticides had a 4.5-fold increased risk of NHL. The risk from pesticides was augmented in women with a family history of cancer [297]. Farm workers exposed to carbamate pesticides, particularly Sevin, have been shown to have a 30–50% increased risk of NHL. In this study, farmers without carbamate pesticide use showed no increased risk of NHL [51].

Hardell & Eriksson [296] carried out a case–control study in Sweden to examine whether phenoxyacetic acids and other pesticides were important factors in the aetiology of NHL. The results showed that exposure to herbicides, particularly 4-chloro-2-methyl phenoxyacetic acid, and fungicides was associated with an increased risk. These findings concurred with a later study by Hardell et al. [291] in which associations were found for 4-chloro-2-methyl phenoxyacetic acid exposure and an increased risk of NHL and hairy cell leukaemia. Zahm et al. [297] demonstrated that rats acutely exposed to 2,4'dichlorophenoxyacetic acid showed severe damage to their lymphoid organs.

Cantor et al. [290] obtained and cryopreserved serum samples from 25,802 participants in the Campaign Against Cancer and Stroke in Washington County, Maryland, USA in 1974. Subsequent analysis of the samples to determine levels of chlordane, lindane,

β-HCH, transnonachlor, heptachlor, heptachlor epoxide, oxychlordane, dieldrin, and HCB in the serum of NHL cases and matched controls found no association with increased NHL risk. However, there was a high coefficient of variation between sample sets in this study compared with their previous study, which may have introduced variance into the odds ratios, and consequently obscured a possible small association. The authors previously found evidence of an increased risk for PCBs but not DDT and related compounds [299].

Overall, there is a wealth of evidence implicating occupational exposure to pesticides and other organochlorines in NHL aetiology. However, is there evidence that background exposure to environmental contaminants may be involved in the aetiology of NHL?

A study by Hardell et al. [300] examined the effect of dioxins and dibenzofurans in a case–control study, which also calculated antibody titres for EBV. The results showed that the concentrations of dioxins and dibenzofurans were similar in cases and controls. However, for some higher chlorinated congeners, an increased risk was found in cases that had high titre to EA IgG (an antibody to EBV). The cases were then divided into two groups: low-grade NHL and high-grade NHL. For TCDD, an increased risk was found in the high-exposure and high-titre group for both categories of NHL. For low-grade NHL, the highest risks were found for cases with EA IgG $>$ 80 and a high concentration of dioxins or furans, but no statistical significance was found. However, cases with high-grade NHL had a significantly increased risk with high antibody titre and high concentrations of 1,2,3,7,8-PeCDD (pentadioxin) and 2,3,4,7,8-PeCDF (pentafuran). For the majority of the higher chlorinated congeners of dioxins and dibenzofurans, an increased risk was found in the high-grade NHL group. The results of this study suggest that current exposure to particular organochlorines in combination with EBV may increase the risk for NHL. These results can be taken to represent background exposure because none of the cases or controls had been occupationally exposed to dioxins or furans.

The authors of the study also found a non-significant decreased risk in the low-titre and high-concentration group for some congeners of dioxins and dibenzofurans, which they state should be noted [300]. A similar previous study by Hardell et al. [292] found an increased risk for hairy cell leukaemia in patients with high antibody titres who were exposed to organic solvents, certain pesticides or impregnating agents compared with those subjects with low antibody levels who were not exposed.

Two studies discussed earlier in this section provide some evidence of background exposure to environmental contaminants and increased risk for NHL. The previously discussed studies in the USA that examined water that was environmentally contaminated with pesticides and nitrates showed an increased risk for NHL following long-term exposure [69,70].

A childhood case–control study carried out by the Children's Cancer Group examined pesticide exposure in the home and risk for NHL. A significant risk for NHL was associated with the frequency of pesticide use in a domestic setting, with professional fumigations in the home, *in utero* and postnatal exposure. Increased risks were observed for T-cell and B-cell lymphomas, for lymphoblastic, large cell, and Burkitt morphologies. The increased risks were found both in young children, less than 6 years old, and in older children. Risks for specific pesticides were not examined in this study [293].

A recent article by Hardell & Eriksson [254] explored the hypothesis that the declining incidence in NHL seen in some developed countries may be a result of cancer prevention methods. The authors reviewed their own work and the work of others in which pesticides, persistent organic pollutants and other organochlorines were associated with an increased risk of NHL. In Sweden, between 1991 and 2000, NHL incidence declined by -0.8 and

−0.2%, respectively, for men and women. Phenoxyacetic acids and chlorophenols, which are pesticides, have been associated with NHL aetiology and these chemicals were banned in 1977. An increasing risk of NHL has also been linked with PCBs, HCB, chlordanes and dioxins. The highest exposure to these substances comes via the food chain, especially from meat and fish. An increased risk for NHL was suggested for high consumers of fish from the Baltic Sea, known to be contaminated by organochlorines [301]. Exposure to these persistent organic pollutants was highest in the 1960s and 1970s. However, there is evidence that the levels have declined, and consequently exposures should have decreased [287]. The levels of these pollutants have probably declined because of regulations put in place during the 1970s. The authors postulated that the change in incidence of NHL in Sweden and the other countries mentioned above could provide a good example of how regulation and precautionary measures to reduce exposure may be reflected in cancer incidence statistics in decades to come [254].

Discussion

There is little doubt that the cell signalling and intracellular control mechanisms required for the orderly co-existence of the different elements of a tissue are capable of being disrupted. Cancer, one of the possible outcomes of such a disruption, has undoubtedly affected multicellular organisms since they first evolved; there is evidence from dinosaur bones of cancerous lesions. The first written evidence of cancer as a disease afflicting *Homo sapiens* dates back to the time of the ancient Greeks and Egyptians. However, questions remain as to whether the incidence rate of cancer in these ancient civilizations was as high as in today's industrialized societies, and the cause of any differences.

Almost 250 years have passed since the first association between cancer and environmental factors was noticed by Percival Pott. Today the widely cited figure is between 1 and 5% of all cancers being attributable to environmental factors [1]. Yet this conservative figure is called into question by twinning studies carried out by Lichtenstein et al. [26] and a mathematical study by Czene et al. [27], which showed that the environment rather than genetics predominates in the aetiology of cancer. Clearly, the environment plays a major role in cancer aetiology.

It has been estimated that up to two-thirds of cancers in developed countries are attributable to tobacco consumption and poor dietary habits [256,302]. It is possible that many of these cancers can be prevented through well thought out prevention measures and education programmes. However, the link between involuntary exposure to environmental contaminants and cancer is complex and it is extremely difficult to find any specific causal links because of this complexity. Thus, prevention measures have to rely on the precautionary principle, usually after the damage has been done.

The incidence of cancer worldwide is set to increase from 2000 levels by 50% by 2020 [3]. In addition, the majority of the increasing burden of cancer in both the developed and the developing world will be suffered by women [303]. Currently, the biggest burden of cancer is seen in affluent developed countries. However, as time passes, the prevalence of cancer is expected to rise in developing countries to similar levels to those found in developed countries [2]. This phenomenon can already be observed for breast cancer incidence [160]. A recent study by Wilson et al. [303], examining the changes in demography in developing nations and the subsequent effect on cancers in women, describes the irony that rising life expectancy in the developing nations, together with the embracing of 'Western' lifestyles, will result in many more people becoming vulnerable to cancer.

Although epidemiological studies do provide some evidence that pollutants may be involved in cancer aetiology, sceptics generally suggest that environmental contaminants, for example synthetic pesticides, which may show some endocrine-disrupting properties, are present at levels too low to cause harm. Thus, we have a vexed question: are humans exposed to environmental pollutants at sufficient levels to be a major factor in cancer aetiology? Some researchers suggest that environmentalists extrapolate results from adult animal tests performed at the maximum tolerable dose, to infer that low doses of the substance would be relevant to human cancer. It is also suggested that the amount of synthetic chemicals, such as pesticides, taken in via the diet pales into insignificance when compared with the amount of natural phytoestrogens taken in [77,122–126]. These two suggestions are flawed. In the first instance, many studies now show that environmentally relevant levels of substances do show responses such as endocrine-disrupting properties. These include low-dose effects following exposure to the environmental oestrogens bisphenol A and DES, where significant non-linear dose responses (U-shape) occurred at a dose lower than the no observed effect level observed by traditional animal testing models [119]. In the second instance, a biochemical mechanism by which relatively tiny amounts of synthetic pesticides may be carcinogenic compared with the relatively huge amounts of natural oestrogenic pesticides was suggested by Bradlow et al. [140].

Another reason given by sceptics is that many of the environmental substances that show oestrogenic properties are not potent oestrogens at low dose. Measuring oestrogenic potency is not sufficient to deem a substance incapable of endocrine disruption. For example, PCBs do not act directly at the oestrogen receptor, but exert their effects indirectly. For example, PCBs have been shown to suppress oestrogen sulphotransferase (SULTE1E1), which is responsible for the inactivation and excretion of oestradiol. Inhibition of this enzyme may increase local levels of oestrogen in oestrogen-sensitive tissues, for example the testis and mammary glands [101].

We should recognize that, despite improving 5-year mortality rates, every case of cancer that occurs is a personal tragedy for the patient and the immediate family. Surviving cancer, particularly childhood cancer, is not necessarily the final sequel. As many as two-thirds of childhood survivors will probably suffer a minimum of one late effect up to 5 years after diagnosis and possibly one quarter of late effects could be life-threatening [304]. Childhood survivors of cancer may face a diminished quality of life as a consequence of treatment toxicity [304–306]. Many parents and adult survivors of childhood cancer may not be fully aware of the possible consequences of their treatment. Table III shows a summary of the long-term side-effects of cancer treatment in childhood [305]. In a 20-year follow-up study,

Table III. Long-term side-effects of childhood cancer therapy. Adapted from [302] (Permission for use granted by Crown Copyright).

Complication	Predisposing factor
Growth retardation	Cranial irradiation
Delayed or precocious puberty	Cranial irradiation
Cognitive deficits	Cranial irradiation
	Intrathecal methotrexate
Subfertility	High-dose cyclophosphamide
	Gonadal irradiation
Cardiomyopathy	Anthracycline use
Second malignancies	Epipodophyllotoxins
	Irradiation
	Alkylating agents

Humpl et al. [307] found a second malignancy rate of 3.25%, which was confirmed by a study by Neglia et al. [308]. In addition, adult survivors of childhood and adolescent cancer show higher death rates compared with their siblings, taking into account the primary cancer as a confounding factor [305]. In the developing world, it is thought that 100,000 children year^{-1} worldwide die needlessly and in pain because of a lack of affordable treatments [309].

As well as the obvious emotional and physical costs of cancer, there is a large economical cost. The cost of treatment and the loss of tax revenue to the economy while the patient undergoes treatment and during recovery is immense. In the UK in 1996, the direct cost of cancer treatment alone amounted to over £1 billion, accounting for about 6% of all National Health Service (NHS) expenditure. Government support for research into cancer is currently about £260 million [310]. The UK NHS Cancer Plan is being supported by the largest ever increase in funding for cancer services. In 2001, the NHS received an extra £280 million to improve cancer services, then a further £127 million in 2002, and by 2003/2004 the NHS was spending £570 million a year more on cancer services than it was in 2000/2001: an increase of 30% [311].

Cancer incidence also places a personal financial burden on families. A study in Australia and New Zealand by Dockerty and colleagues [312], which investigated the economic effects of childhood cancer on families, concluded that there is a large financial burden on families who have a child with cancer. Studies in the UK and USA came to the same conclusion. The mean total additional cost to families was around 13% of the family income. For eight of the families that took part in the study, the extra expenses amounted to 50% of the total family income [313,314].

There is mounting animal (experimental and wildlife) and human epidemiological evidence that environmental contaminants, particularly persistent organic chemical contaminants, are involved in the aetiology of cancer and that these chemicals exert their carcinogenicity at a time of development (prenatal, childhood, and adolescence). Thus, preventative measures to protect all people need to be put into place. An overall exposure reduction of bioaccumulative, persistent, carcinogenic and/or endocrine-disrupting chemicals should be planned. This should be based on the precautionary principle, thus accepting that there can be no reasonable prospect of identifying individual environmental pollutants as being the specific cause of particular tumours because of the complex mixture to which humans are exposed. Action will have to be taken in the absence of absolute scientific certainty.

In 1999, the Third European Ministerial Conference on Environment and Health, held in London, requested, in Paragraph 50 of the declaration, that the WHO should

> promote and encourage public health measures into areas of emerging concern to children's health on the basis of the precautionary principle.

It also states in the declaration

> We recognize that exposure prevention is the most effective means of protecting children from environmental threats to health and we will develop prevention-oriented policies and actions [315].

In a poster by von Ehrenstein et al. [269] the authors point out that a good example of a precautionary approach related to children's health protection is the European Union ban

on phthalates, which have been shown to have adverse health effects on the developing male reproductive tract and may be carcinogenic in humans. Phthalates were widely used as a plasticizer in PVC products. Many of these are products used specifically by children and infants, for example feeding bottles and plastic toys [316]. The ban is only in force until research provides conclusive data. It may make good health policy if this type of ban was used for all novel chemical substances and no exemptions were granted.

In a recent article, Hardell & Eriksson [254] noticed that NHL incidence declined in Sweden by −0.8 and −0.2%, respectively, for men and women during 1991–2000. They reasoned that the decline in NHL incidence may be a direct result of prevention measures put in place in Sweden in the 1970s. Phenoxyacetic acids and chlorophenols, which are pesticides, have been associated with NHL aetiology and these chemicals were banned in 1977.

It is feasible that chemical environmental contaminants, in particular synthetic pesticides and organochlorines with endocrine-disrupting properties, could be major factors in cancer aetiology, particularly hormone-dependent malignancies such as breast, testicular and prostate cancers. The endocrine-disrupting properties of these compounds can perturb organogenesis and other developmental processes, such as mammary gland development. It would seem that there are critical windows during developmental processes when endocrine-disrupting chemicals can exert their effects and initiate cancers; for example, during female mammary gland development and male reproductive tract development. A chemical may have an adverse effect at one point in time but before or after that point in time the chemical may have no effects at all. Some similar reviews conclude that environmental exposures to carcinogenic or endocrine-disrupting chemicals exist at concentrations too low or have carcinogenic potential too weak to be considered a major factor in cancer aetiology. However, the evidence discussed in this review would dispute that claim; even if healthy adults are not at risk, it would seem that the developing foetus, infant, child and young adult are at risk. Studies discussed in this review show that low oestrogenic potency cannot be used as a marker of the capability of a chemical to cause oestrogenic responses and endocrine disruption.

As well as the timing of exposure, other variables need to be considered. Many people have genetic polymorphisms that may render them more susceptible to cancer initiation than a wild-type person following exposure to a substance with low oestrogenic potency. For example, the gene product *p53* may have a modifying effect on organochlorine influence on breast cancer risk [195]. Women with at least one variant of the CYP1A1-exon 7 genotype have an increased risk of breast cancer associated with high serum levels of PCBs [193]. Unknown genetic susceptibility to cancer may account for a large proportion of the population. In addition, exposure to environmental pollutants may affect how aggressive the tumour is, possibly adversely affecting the prognosis.

Without doubt, governments and health organizations should be concerned about the increase in cancer incidence. Preventative measures other than education about tobacco, diet and the promotion of physical activity should be considered. Moreover, it seems to be the most vulnerable members of society, the developing foetus, the developing child and the adolescent, that are at risk of developing cancer following involuntary exposure to environmental contaminants. This may be an appropriate time for governments to adopt the precautionary principle, until all substances to which members of society are involuntarily exposed are proved safe from long-term, low-level effects on human and wildlife health, rather than treating the consequences. Moreover, the estimation that between 1 and 5% of malignant disease in developed countries is attributable to environmental factors may need revising upwards.

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